#14

PATENT
Atty. Docket No.: 9009.0008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,776,944

Issued: July 7, 1998

To: Chang Y. Hong, Young K. Kim, Se H. Kim, Jay H. Chang, Hoon Choi, Do H. Nam, Ae R. Kim, Jin H. Lee, Ki S. Park

Assignee: LG Life Sciences, Ltd.

For: 7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROPLIDIN-1-YL)-1-CYCLOPROPYL-6-FLUORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF

MAIL STOP: PATENT EXT.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Applicant, LG Life Sciences, Ltd., represents that it is the Assignee of the entire interest in and to United States Patent No. 5,776,944 granted to Chang Y. Hong, Young K. Kim, Se H. Kim, Jay H. Chang, Hoon Choi, Do H. Nam, Ae R. Kin, Jin H. Lee, and Ki S. Park on the 7th day of July, 1998, for 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and the process for the preparation thereof by virtue of an assignment in favor of LG Life Sciences, Ltd. An assignment from the inventors to LG Chemical Ltd. was recorded at Reel 007531, Frame 0413 on June 15, 1995. A document indicating a change in name from LG Chemical Ltd. to LG Chem Investment, Ltd. was recorded at Reel

013563, Frame 0644 on December 11, 2002. An assignment from LG Chem Investment, Ltd. to LG Life Sciences, Ltd. was recorded at Reel 013570, Frame 0131 on December 11, 2002. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints attorneys at Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., associated with Customer No. 22852, including Charles E. Van Horn, Andrew C. Sonu and Steven P. O'Connor, as attorneys for LG Life Sciences, Ltd. with regard to this application for extension of the term of U.S. Patent 5,776,944 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Information Required Under 37 C.F.R. § 1.740

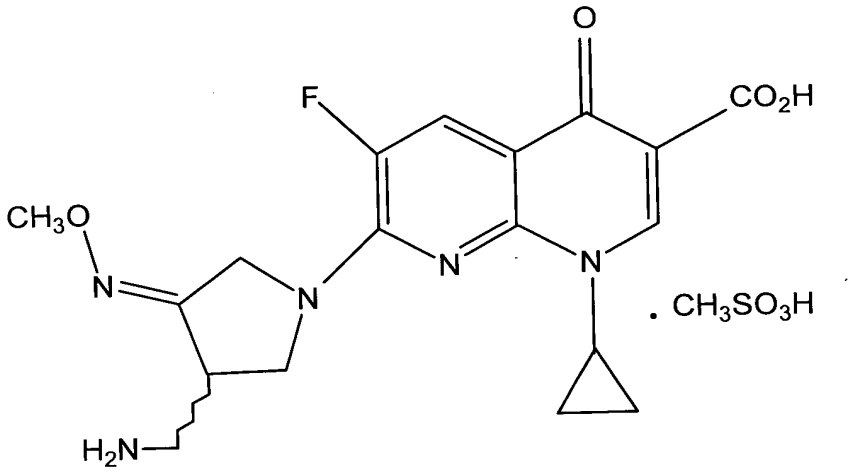
Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product FACTIVE® is a broad spectrum antibacterial agent for oral administration containing gemifloxacin mesylate as the active ingredient. Gemifloxacin is available as the mesylate salt in the sesquihydrate form. Identification of gemifloxacin is as follows:

Chemical Name(s): (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino}-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

Empirical Formula of gemifloxacin mesylate: $C_{18}H_{20}FN_5O_4 \bullet CH_4O_3S$

Structural Formula of gemifloxacin mesylate:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505.

(3) The approved product FACTIVE® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on April 4, 2003. A copy of the approval letter is attached (Attachment B).

(4) The active ingredient in FACTIVE® is gemifloxacin mesylate available in the sesquihydrate form which, on information and belief, has not been approved for commercial marketing or use under the Public Health Services Act, the Virus-Serum-Toxin Act or under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 21-158 by the Food and Drug Administration on April 4, 2003. A copy of the approved labeling information describing the approved product is attached (Attachment C).

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on June 3, 2003.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Chang Y. Hong, Young K. Kim, Se H. Kim,
Jay H. Chang, Hoon Choi, Do H. Nam,
Ae R. Kim, Jin H. Lee, Ki S. Park

Patent No.: 5,776,944

Issue Date: July 7, 1998

Expiration Date: June 15, 2015

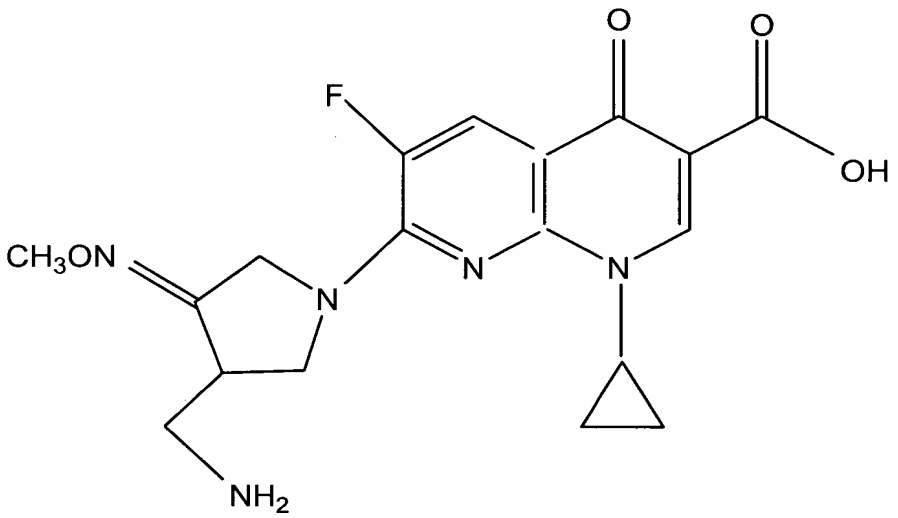
(7) A true copy of the patent is attached (Attachment D).

(8) No reexamination certificate or certificate of correction has been issued on this patent. LG Life Sciences, Ltd. filed a request for reexamination of U.S. Patent No. 5,776,944 on December 27, 2002, which was granted by the U.S. Patent

and Trademark Office by an Order mailed February 20, 2003. The reexamination control number is 90/006,498. A copy of a record of maintenance fee payment under 35 U.S.C. § 41(b) is attached (Attachment E).

(9) Claims 1-7 of U.S. Patent 5,776,944 claim the active ingredient in FACTIVE®. Claims 8-12 are directed to a process for preparing the active ingredient in FACTIVE®. Claims 13-16 are directed to an antibacterial composition comprising the active ingredient in FACTIVE®.

(a) Claim 1 reads as follows: "7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid represented by the following formula:

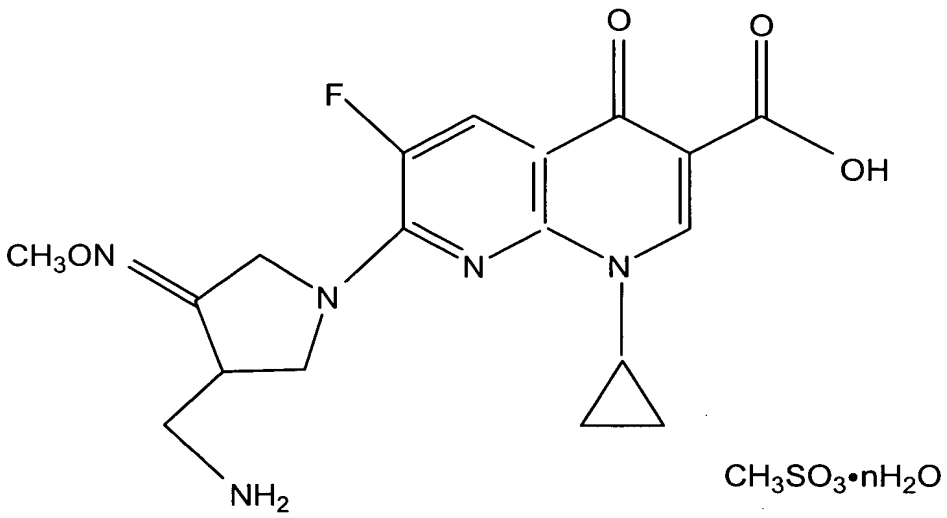


or a pharmaceutically acceptable non-toxic salt, physiologically hydrolyzable ester, or isomer thereof."

Claim 1 reads on the active ingredient in FACTIVE®.

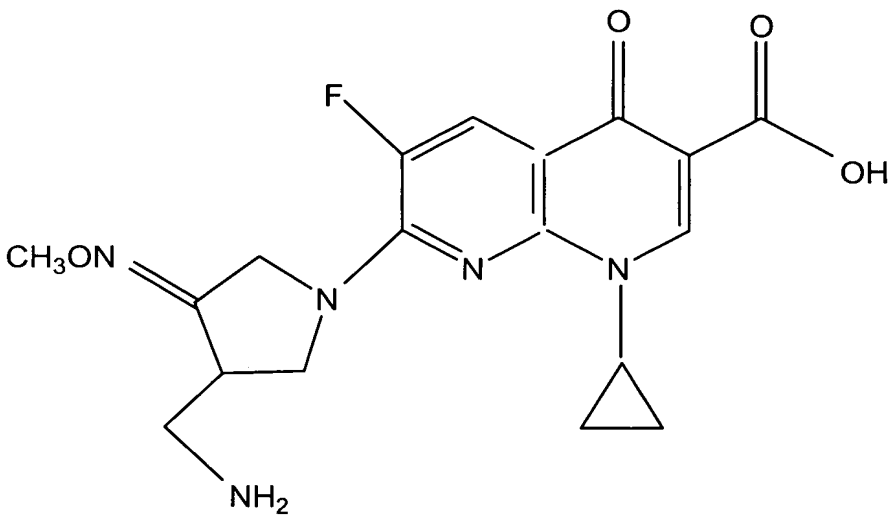
(b) Claim 3 reads as follows: "7-(4-aminomethyl-3-

methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof represented by the following formula:

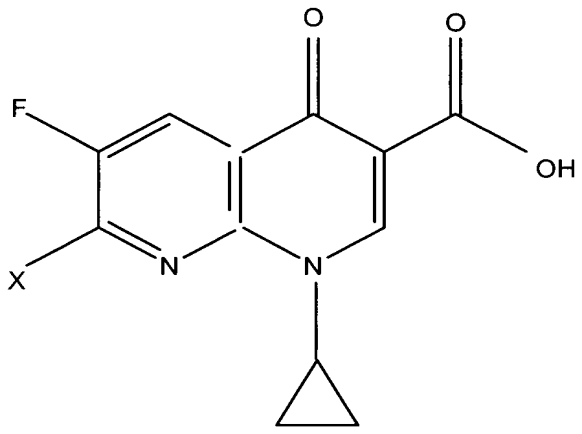


or its isomer, in which n denotes 0, 1, 1.5, 2, 2.5, 3, 3.5 or 4; or an isomer thereof." Claim 3 reads on the sesquihydrate form of the active ingredient of FACTIVE® when n is 1.5

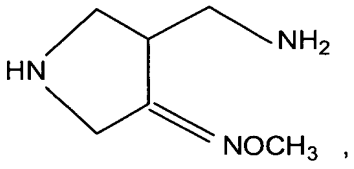
(c) Claim 8 reads as follows: "A process for preparing 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid represented by the following formula:



or its isomer, methanesulfonate and hydrate of the methanesulfonate, which comprises reacting a quinolone compound represented by the following formula,



in which X represents a halogen, with a pyrrolidine oxime compound represented by the following formula, or a salt thereof,



,

in a solvent in the presence of an acid acceptor."

Claim 8 reads on a process for preparing the active ingredient in FACTIVE®.

(d) Claim 13 reads as follows: "An antibacterial composition comprising as an active component the compound defined in claim 1, together with a pharmaceutically acceptable carrier." Claim 13 similarly reads on the approved product FACTIVE® because the product contains a compound of claim 1 as explained above and a pharmaceutically acceptable carrier (inactive ingredients such as hydroxypropyl methylcellulose).

(e) Claim 15 reads as follows: "An antibacterial composition comprising as an active component the compound defined in claim 3, together with a pharmaceutically acceptable carrier." Claim 15 similarly reads on the approved product FACTIVE® because the product contains a compound of claim 3 as explained above and a pharmaceutically acceptable carrier (inactive ingredients such as hydroxypropyl methylcellulose).

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 53,908) for FACTIVE® was submitted on August 6, 1997, received on August 7, 1997, and became effective on September 6, 1997.

New Drug Application for FACTIVE® (NDA 21-158) was submitted on December 15, 1999.

New Drug Application for FACTIVE® (NDA 21-158) was approved on April 4, 2003.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to FACTIVE® and the dates applicable to these significant activities are set forth in a chronology of events in Attachment F.

(12)(i) Applicant is of the opinion that U.S. Patent 5,776,944 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent 5,776,944 claims a drug product, that is, the active ingredient in FACTIVE® and antibacterial compositions comprising the active ingredient.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent 5,776,944 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 5,776,944 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The product FACTIVE® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the product FACTIVE® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (*i.e.*, Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the product FACTIVE®. Applicant has filed two other applications for term extension (U.S. Patent Nos. 5,633,262 and 5,962,468) based on the regulatory review period for the product FACTIVE. Applicant will make an election of only one patent in accordance with 37 CFR 1.785(b) upon receipt of a notice of final determination in these applications from the Patent and Trademark Office.

(12)(ii) Applicant respectfully submits that the length of the extension of patent term for U.S. Patent 5,776,944 is 659 days pursuant to 35 U.S.C. § 156(c). The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on September 6, 1997 and ended on April 4, 2003, which is a total of 2038 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on September 6, 1997 and ended on December 15, 1999, which is 831 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", began on December 15, 1999, and ended on April 4, 2003, which is a total of 1207 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (2038) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (July 7, 1998) which is 304 days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in subparagraph (12)(ii)(a)(1) above after the patent issued (one-half of 527) which is 263 days;

(c) The number of days as determined in subparagraph (12)(ii)(b) (1471 days) when added to the original term of the patent (June 15, 2015) would result in the date of June 15, 2019.

(d) Fourteen (14) years when added to the date of the NDA approval (April 4, 2003) would result in the date of April 4, 2017;

(e) The earlier date as determined in subparagraphs (12)(ii)(c) and (12)(ii)(d) is April 4, 2017;

(f) Since the patent for FACTIVE® issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of June 15, 2015. Five years when added to the original expiration date of the patent would result in the date of June 15, 2020.

(g) The earlier date as determined by subparagraphs (12)(ii)(e) and (12)(ii)(f) is April 4, 2017.

(13) Applicant acknowledges a duty to disclose to the Director of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this application is attached as a check in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Charles E. Van Horn
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315
Phone: 202-408-4000
Fax: 202-408-4400

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof (Attachment G).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: May 29, 2003

Attachments:
Power of Attorney (Attachment A)
Approval Letter (Attachment B)
Approved Labeling Information for FACTIVE® (Attachment C)
U.S. Patent 5,776,944 (Attachment D)
Maintenance Fees Paid (Attachment E)
Chronology of Regulatory Review Period (Attachment F)
Certification of Copies of Application Papers (Attachment G)

A

PATENT
Atty. Docket No.: 9009.0008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,776,944)
)
Issued: July 7, 1998)
)
To: Chang Y. Hong, Young K. Kim, Se. H. Kim,)
Jay H. Chang,, Hoon Choi, Do H. Nam,)
Ae R. Kim, Jin H. Lee, Ki S. Park)
)
Assignee: LG Life Sciences, Ltd.)

For: 7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROPLIDIN-1-YL)-1-CYCLOPROPYL-6-FLUORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF

MAIL STOP: PATENT EXT.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

POWER OF ATTORNEY

LG Life Sciences, Ltd. represents that it is the assignee of the above-identified U.S. Letters Patent by virtue of an assignment from the inventors to LG Chemical Ltd. was recorded at Reel 007531, Frame 0413 on June 15, 1995. A document indicating a change in name from LG Chemical Ltd. to LG Chem Investment, Ltd. was recorded at Reel 013563, Frame 0644 on December 11, 2002. An assignment from LG Chem Investment, Ltd. to LG Life Sciences, Ltd. was recorded at Reel 013570, Frame 0131 on December 11, 2002. LG Life Sciences, Ltd. hereby grants the power of attorney to the attorneys of **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, associated with Customer No. 22852 including Charles E. Van Horn, Reg. No. 40,266; Andrew C. Sonu, Reg. No. 33,457; and Steven P. O'Connor, Reg. No. 41,225; both jointly

and separately to be attorneys for LG Life Sciences, Ltd. with regard to an application for extension of the term of U.S. Patent 5,776,944 and to transact all business in the Patent and Trademark Office and Food and Drug Administration connected therewith.

Please send all future correspondence concerning the above matter to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., at the following address:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

The undersigned is empowered to sign this power and statement of ownership on behalf of the assignee.

LG Life Sciences, Ltd.

Date: May 23, 2003

Ji-Yong Song
Executive Vice President

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

B

NDA 21-158

LG Life Sciences, Ltd
C/o PAREXEL International
Attention: Gail Glifort
2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713

Dear Ms. Glifort:

Please refer to your new drug application (NDA) dated December 15, 1999, received December 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Factive (gemifloxacin mesylate) Tablets, 320 mg.

We acknowledge receipt of your submissions dated as follows:

October 14, 2002	December 16, 2002	February 12, 2003
October 24, 2002	December 20, 2002	February 17, 2003
October 29, 2002	December 30, 2002 (2)	February 18, 2003
October 30, 2002	January 2, 2003	February 20, 2003
October 31, 2002	January 9, 2003	February 21, 2003
November 1, 2002	January 10, 2003	February 27, 2003 (2)
November 4, 2002	January 16, 2003	March 24, 2003
November 14, 2002	January 22, 2003	March 27, 2003
November 25, 2002	January 24, 2003	March 28, 2003 (2)
November 26, 2002	January 30, 2003	April 4, 2003
December 9, 2002 (3)	January 31, 2003	
December 12, 2002	February 11, 2003	

Your October 4, 2002 submission constituted a complete response to our December 15, 2000 action letter.

This new drug application provides for the use of Factive (gemifloxacin mesylate) Tablets for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis.

We have completed the review of this application, as amended. We have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved for these indications, effective on the date of the letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted April 3, 2003) and the agreed-upon labeling (immediate container and carton labels submitted March 28, 2003 to be amended as agreed during our April 2, 2003 teleconference and as stated in your April 3, 2003 submission). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the

FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **FPL for approved NDA 21-158.**? Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated March 28, 2003:

1. Comparative Safety Study

   Conduct a prospective, randomized study comparing gemifloxacin (5,000 patients) to an active control (2,500 patients) in patients with community-acquired pneumonia (CAP) or acute bacterial exacerbation of chronic bronchitis (ABECB). At least 10% of patients should be of African origin, 10% of Asian origin and 10% of Hispanic origin to gain safety information in other minority or ethnic groups, specifically as it relates to rash. Patients should be evaluated for clinical and laboratory safety.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 11 months of the date of this letter
Interim Report Submission:	Within 12 months of date of this letter (with the annual report)
Final Report Submission:	Within 4 years of the initiation of the study

2. Prescribing Patterns and Use

   Conduct a study to evaluate the prescribing patterns and use of gemifloxacin. In this study, obtain data on the prescribing patterns and use of gemifloxacin for the first three years after initial marketing in the US. Include the number of prescriptions issued (as well as the rate of refills) and the diagnoses for which the prescriptions were dispensed. These data may be obtained from various databases such as HMOs, governmental agencies, and pharmacy organizations.

Protocol Submission:	Within 4 months of the date of this letter
Interim Report Submission:	Within 12 months of date of this letter (with the annual report)
Final Report Submission:	Within 5 years of date of this letter

The Division anticipates discussing the details of the above studies at your earliest convenience.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **Postmarketing Study Protocol? 밿ostmarketing Study Final Report? or 밿ostmarketing Study Correspondence.**

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In

any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-158 for this drug product. We also note that you agreed to evaluate spontaneously reported adverse events, particularly for the cutaneous, hepatic, musculoskeletal, and cardiac (conducting system) organ systems, annually for the first three years after initial marketing in the US.

If you have any questions, call Yon Yu, Pharm. D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

C

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Goldberger
4/4/03 03:23:47 PM

FACTIVE

Gemifloxacin mesylate

(SB-265805)

Item 2 Labeling

LG Life Sciences Final Draft Version as of April 4, 2003

Prescribing Information (Non-annotated)

April 3, 2003 version

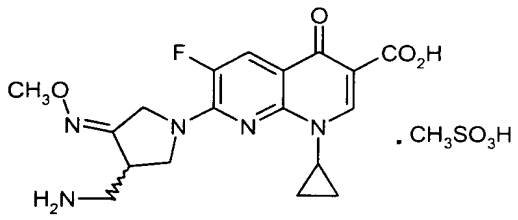
PRESCRIBING INFORMATION

FACTIVE® brand of gemifloxacin mesylate tablets.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]- 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/mL at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$ and its chemical structure is:



Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral

doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (Cmax) and systemic drug exposure (AUC(0-24)) were 1.61 ± 0.51 μg/mL (range 0.70-2.62 μg/mL) and 9.93 ± 3.07 μg•hr/mL (range 4.71-20.1 μg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 μg•hr/mL; range 3.2 – 47.7 μg•hr/mL.

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the in vivo plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 – 12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:

Table 1

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean±SD)
Plasma	1.40 (0.442) µg/mL	---
Bronchoalveolar Macrophages	107 (77) µg /g	90.5 (106.3)
Epithelial Lining Fluid	2.69 (1.96) µg /mL	1.99 (1.32)
Bronchial Mucosa	9.52 (5.15) µg /g	7.21 (4.03)

Metabolism

Gemifloxacin its metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component d
etected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

Excretion

Gemifloxacin and it metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61± 9.5% of the dose was excreted in the feces and 36± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

Special Populations

Pediatric: The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin,

AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 μg·h/mL (range, 3.21 – 42.71 μg·h/mL) and 8.80 μgg·h/mL (range, 3.33 – 47.73 μg·h/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34% and a mean increase in Cmax of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC (0-inf) of 45% and a mean increase in Cmax of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential: In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg b.i.d., or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg b.i.d. and the photosensitivity potential for

both drugs were statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS**).

Drug-Drug Interactions

Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum-and magnesium- containing antacid is concomitantly administered (AUC decreased 85%; Cmax decreased 87%. Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking FACTIVE tablets.

Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21% and Cmax decreased].

Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS.**)

In Vitro Metabolism: Results of in vitro inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant in vivo pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300 to 400 mg b.i.d. to healthy male subjects).

Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average

reduction in gemifloxacin AUC and Cmax of 19% and 12%. These changes are not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 μg/150 μg once daily for 21 days to healthy female subjects).

Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin Time). (See **PRECAUTIONS: Drug Interactions.**)

Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin Cmax increased 8%.

Microbiology

Gemifloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.
The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones.

There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Streptococcus pneumoniae (including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL)

Aerobic gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae (many strains are only moderately susceptible)
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following data are available, **but their clinical significance is unknown**.

Gemifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of (0.25 µg/mL) or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Acinetobacter lwoffi
Klebsiella oxytoca

Legionella pneumophila
Proteus vulgaris

SUSCEPTIBILITY TESTS

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5	Intermediate (I)
≥1.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [a]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae* [b]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)
0.25	Intermediate (I)

≥0.5	Resistant (R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation –adjusted Muller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values:

Microorganism		MIC Range (µg/mL)
Enterococcus faecalis	ATCC 29212	0.016-0.12
Escherichia coli	ATCC 25922	0.004-0.016
Haemophilus influenzae	ATCC 49247[c]	0.002-0.008
Streptococcus pneumoniae	ATCC 49619[d]	0.008-0.03

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)[1].

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5μg gemifloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
16-19	Intermediate (I)
≤15	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [e]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[e] This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae* [f]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

[f] These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gemifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5μg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-36
Haemophilus influenzae	ATCC 49247[g]	30-37
Streptococcus pneumoniae	ATCC 49619[h]	28-34

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2] .

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

FACTIVE is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES**).

Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis.*

Community-acquired pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥2μg/mL), *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Klebsiella pneumoniae**.

* In the clinical trials, there were 13 subjects with *Klebsiella pneumoniae*, primarily from non-comparative studies. 10 subjects had mild disease, 2 had moderate disease, and 1 had severe disease. There were two clinical failures in subjects with mild disease (one of these had a bacteriologic recurrence).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gemifloxacin is contraindicated in patients with a history of hypersensitivity to gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy and Nursing Mothers subsections.)

QT Effects: **GEMIFLOXACIN MAY PROLONG THE QT INTERVAL IN SOME PATIENTS. GEMIFLOXACIN SHOULD BE AVOIDED IN PATIENTS WITH A HISTORY OF PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED ELECTROLYTE DISORDERS (HYPOKALEMIA OR HYPOMAGNESEMIA), AND PATIENTS RECEIVING CLASS IA (E.G., QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G., AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS.**

Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gemifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gemifloxacin treatment in over 6775 patients, including 653 patients concurrently receiving drugs known to prolong the QTc interval and 5 patients with hypokalemia.

The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oral administration of gemifloxacin.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Gemifloxacin should be discontinued immediately at the appearance of any sign of an immediate type I hypersensitivity skin rash or any other manifestation of a hypersensitivity

reaction; the need for continued fluoroquinolone therapy should be evaluated. As with other drugs, serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and occasionally fatal events, some due to hypersensitivity and/or some of uncertain etiology, have been reported in patients receiving fluoroquinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations usually include new onset fever and one or more of the following: rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Tendon and Cartilage Effects: Fluoroquinolones as a class have been shown to cause arthropathy and osteochondrosis in immature rats and dogs. The relevance of these findings to humans is unknown.
Tendonitis and rupture of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving fluoroquinolones. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur either during or after treatment. Elderly patients, athletes, and patients taking corticosteroids are more prone to tendonitis.

CNS Effects: In clinical studies with gemifloxacin, Central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, gemifloxacin should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in gemifloxacin clinical trials, convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving other fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving gemifloxacin, the drug should be discontinued and appropriate measures instituted.

Antibiotic Associated Colitis: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gemifloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See **ADVERSE REACTIONS.**)

PRECAUTIONS

General: Prescribing FACTIVE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increase the risk of the development of drug-resistant bacteria.

Rash: In clinical studies, the overall rate of drug-related rash was 2.8%. The most common form of rash associated with gemifloxacin was described as maculopapular and mild to moderate in severity; 0.3% were described as urticarial in appearance. Rash usually appeared 8 to 10 days after start of therapy; 60% of the rashes resolved within 7 days, and 80% resolved within 14 days. Approximately 10% of those patients developing rash had a rash described as of severe intensity. Histology was evaluated in a clinical pharmacology study and was consistent with an uncomplicated exanthematous skin reaction and showed no evidence of phototoxicity, vasculitis, or necrosis. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). Prolonging duration of therapy beyond 7 days causes the incidence of rash to increase significantly in all subgroups except men over the age of 40 (see Table 2). Gemifloxacin therapy should be discontinued in patients developing a rash while on treatment (see **ADVERSE REACTIONS** and **CLINICAL STUDIES**).

Table 2. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies Population* by Gender, Age, and Duration of Therapy

Gender & Age (yr) Category	Duration of Gemifloxacin Therapy			
	5 days	7 days	10 days**	14 days**
Female < 40	5/242 (2.1%)	39/324 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	19/1210 (1.6%)	30/695 (4.3%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	4/218 (1.8%)	20/318 (6.3%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥ 40	9/1321 (0.7%)	23/776 (3.0%)	9/345 (2.6%)	3/116 (2.6%)
Totals	37/2991 (1.2%)	112/2113 (5.3%)	55/858 (6.4%)	23/312 (7.4%)

*includes patients from studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and other indications.
exceeds the recommended duration of therapy (see **DOSAGE AND ADMINISTRATION)

Photosensitivity reactions have been reported very rarely in clinical trials with FACTIVE. (See **CLINICAL PHARMACOLOGY.**) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.

Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving gemifloxacin 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of elevations in liver enzymes. (See **ADVERSE REACTIONS.**)

There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of gemifloxacin 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See **DOSAGE AND ADMINISTRATION.**)

Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤40 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

Adequate hydration of patients receiving gemifloxacin should be maintained to prevent the formation of a highly concentrated urine.

Information for Patients:
Patients should be advised:

- that antibacterial drugs including FACTIVE should only be used to treat bacterial infections. They do not treat viral infections (e.g. common cold). When FACTIVE is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance.

- that FACTIVE has been associated with rash. Patients should discontinue drug and call their healthcare provider if they develop a rash.

- that FACTIVE may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose; patients should immediately discontinue the drug at the sign of a rash or other allergic reaction and seek medical care;

- that FACTIVE may produce changes in the electrocardiogram (QTc interval prolongation);

- that FACTIVE should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;

- that FACTIVE should be used with caution in patients receiving drugs that may affect the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants;

- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia;

- to inform their physician of any other medications when taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;

- to contact their physician if they experience palpitations or fainting spells while taking FACTIVE;

- that FACTIVE may be taken with or without meals;

- to drink fluids liberally;

- not to take antacids containing magnesium and/or aluminum or products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or

Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution within 3 hours before or 2 hours after taking FACTIVE tablets;

- that FACTIVE should be taken at least 2 hours before sucralfate;
- that phototoxicity has been reported with certain quinolones. The potential for FACTIVE to cause phototoxicity was low (3/7659) at the recommended dose in clinical studies. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);
- that FACTIVE may cause dizziness; if this occurs, patients should not operate an automobile or machinery or engage in activities requiring mental alertness or coordination;
- that they should discontinue FACTIVE therapy and inform their physician if they feel pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until the diagnosis of tendonitis or tendon rupture has been excluded;
- that convulsions have been reported in patients receiving quinolones; and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: Administration of repeat doses of FACTIVE had no effect on the repeat dose pharmacokinetics of theophylline, digoxin or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**.)

Concomitant administration of FACTIVE and calcium carbonate, cimetidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. (See **CLINICAL PHARMACOLOGY.**)

Concomitant administration of FACTIVE with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. (See **CLINICAL PHARMACOLOGY**.)

FACTIVE had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, because some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in patients, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after FACTIVE. Sucralfate should not be taken within 2 hours of FACTIVE. (See **CLINICAL PHARMACOLOGY.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.

Photocarcinogenesis: Gemifloxacin did not shorten the time to development of UVR-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in this model. These mice received oral gemifloxacin and concurrent irradiation with simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately 1/3 of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per day, the mice had skin gemifloxacin concentrations of approximately 7.4 μg/g. Plasma levels following this dose were approximately1.4 μg/mL in the mice around the time of irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse plasma gemifloxacin levels are in the expected range of human plasma Cmax levels (0.7-2.6 μg/mL, with an overall mean of about 1.6 μg/mL) following multiple 320 mg oral doses.

Mutagenesis: Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic in vitro in the mouse lymphoma and human lymphocyte chromosome aberration assays. It was clastogenic *in vivo* in the rat micronucleus assay at oral and intravenous dose levels (≥800 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity. Fluoroquinolone clastogenicity is apparently due to inhibition of mammalian topoisomerase activity which has threshold implications.

Impairment of Fertility: Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration (216 and 600 mg/kg/day) that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day) at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared to be reversible in a pre- and postnatal development study (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons) caused fetal brain and ocular malformations in the presence of maternal toxicity. The overall no-effect exposure level in pregnant animals was approximately 0.8 to 3-fold clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

Pediatric Use

Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy and osteochondrosis in immature animals. (See **WARNINGS.**)

Geriatric Use

Of the total number of subjects in clinical studies of gemifloxacin, 30% (2064) were 65 and over, while 12% (779) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rates for this group was similar to or lower than that for younger subjects with the exception that the incidence of rash was lower in geriatric patients compared to patients less than 40 years of age.

ADVERSE REACTIONS

In clinical studies, 6775 patients received daily oral doses of 320 mg gemifloxacin. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of gemifloxacin in clinical pharmacology studies. The majority of adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

Gemifloxacin was discontinued because of an adverse event (possibly or probably related) in 2.2% of patients, primarily due to rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria

(0.3%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%).

Drug-related adverse events, classified as possibly or probably related with a frequency of ≥1% for patients receiving 320 mg of gemifloxacin or comparator drug are presented in Table 3.

Table 3

	Gemifloxacin 320mg N=6775 %	All oral comparators* N=5248 %
Diarrhea	3.6	4.6
Rash	2.8	0.6
Nausea	2.7	3.2
Headache	1.2	1.5
Abdominal pain	0.9	1.1
Vomiting	0.9	1.1
Dizziness	0.8	1.5
Taste perversion	0.3	1.9

*beta-lactam antibiotics, macrolides, and other fluoroquinolones.

Gemifloxacin appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

Additional drug-related adverse events (possibly or probably related) in >0.1% to 1% of patients who received 320 mg of gemifloxacin were: abdominal pain, anorexia, arthralgia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, hyperglycemia, insomnia, leukopenia, moniliasis, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≤0.1% of patients were: abnormal urine, anemia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, flushing, gastroenteritis, granulocytopenia, hot flashes, increase GGT, leg cramps, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, pneumonia, thrombocyotopenia, tremor, vertigo, and vision abnormality.

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidences of rash were as follows (Table 4):

Table 4

	ABECB (5 days) N = 2284		CAP (7 days) N = 643	
	n/N	%	n/N	%
Totals	27/2284	1.2	26/643	4.0
Females, < 40 years	NA*		8/88	9.1
Females, ≥ 40 years	16/1040	1.5	5/214	2.3
Males, < 40 years	NA*		5/101	5.0
Males, ≥ 40 years	11/1203	0.9	8/240	3.3

* insufficient number of patients in this category for a meaningful analysis

(see **PRECAUTIONS**)

Laboratory Changes: The percentages of patients who received multiple doses of gemifloxacin and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to gemifloxacin or an underlying condition.

Clinical Chemistry: increased ALT (1.5%), increased AST (1.1%), increased creatine phosphokinase (0.6%), increased potassium (0.5%), decreased sodium (0.3%), increased gammaglutamyl transferase (0.5%), increased alkaline phosphatase (0.3%), increased total bilirubin (0.3%), increased blood urea nitrogen (0.3%), decreased calcium (0.2%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased total protein (0.1%) and increased calcium (<0.1%).

CPK elevations were noted infrequently: 0.8% in gemifloxacin patients vs. 0.4% in the comparator patients.

Hematology: increased platelets (0.9%), decreased neutrophils (0.5%), increased neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2 %), decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

In clinical studies, approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 10% showed a further elevation of their ALT at the on-therapy visit and 5% showed a further elevation at the end of therapy visit. None of these patients demonstrated evidence of hepatocellular jaundice. For the pooled comparators, approximately 6% of patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 7% showed a further elevation of their ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

In a clinical trial where 638 patients received either a single 640 mg dose of gemifloxacin or 250 mg bid of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm (1.0%). In this study, two patients experienced ALT elevations of 8 to10 times the upper limit of normal. These elevations were asymptomatic and reversible.

OVERDOSAGE

Any signs or symptoms of overdosage should be treated symptomatically. No specific antidote is known. In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically with appropriate hydration maintained. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and clonic convulsions.

DOSAGE AND ADMINISTRATION

FACTIVE can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of FACTIVE is 320 mg daily, according to the following table (Table 5).

Table 5

INDICATION	DOSE	DURATION
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia (of mild to moderate severity)	One 320 mg tablet daily	7 days

The recommended dose and duration of FACTIVE should not be exceeded (see Table 2).

Renally Impaired Patients: Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. Table 6 provides dosage guidelines for use in patients with renal impairment:

Table 6. RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤40	160 mg q24h

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg q24h.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men

Use in Hepatically Impaired Patients: No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Use in Elderly: No dosage adjustment is recommended.

HOW SUPPLIED

FACTIVE (gemifloxacin mesylate) is available as white to off-white, oval, film-coated tablets with breaklines and GE 320 debossed on both faces. Each tablet contains gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

320 mg Unit of Use (CR*) 5's	NDC 67707-320-05
320 mg Unit of Use (CR*) 7's	NDC 67707-320-07
320 mg Hospital Pack (NCR**) 30's	NDC 67707-320-30

*Child Resistant
** Not Child Resistant

STORAGE

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. Degeneration of articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in a 28-day study (producing about 6 times the systemic exposure at the clinical dose), but not in mature dogs. There was no damage to the articular surfaces of joints in immature rats given repeated doses of up to 800 mg/kg/day.

Some quinolones have been reported to have proconvulsant properties that are potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs). Gemifloxacin alone had effects in tests of behaviour or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and local periportal liver changes associated with blockage of small bile ducts by crystals containing gemifloxacin.

Quinolones have been associated with prolongation of the electrocardiographic QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed orally to provide about 4 times human therapeutic plasma concentrations at Cmax, and transient prolongation after intravenous administration at more than 4 times human plasma levels at Cmax. Gemifloxacin exhibited weak activity in the cardiac I_{Kr} (hERG) channel inhibition assay, having an IC_{50} of approximately 270 μM.

Gemifloxacin, like many other quinolones, tends to crystallise at the alkaline pH of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal (oral no-effect dose 24 mg/kg/day).

Gemifloxacin was weakly phototoxic to hairless mice given a single 200 mg/kg oral dose and exposed to UVA radiation, however, no evidence of phototoxicity was observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model, using simulated sunlight.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

FACTIVE (320 mg once daily for 5 days) was evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal double-blind, randomized, actively-controlled clinical trials (studies 068, 070, and 212). The primary efficacy parameter in these studies was the clinical response at follow-up (day 13 to 24). The results of the clinical response at follow-up for the principal ABECB studies demonstrate that FACTIVE 320 mg

PO once daily for 5 days was at least as good as the comparators given for 7 days. The results are shown in Table 7 below.

Table 7. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
Study 068		
FACTIVE 320 mg x 5 days	86.0 (239/278)	1.2 (-4.7, 7.0)
Clarithromycin 500 mg bid x 7 days	84.8 (240/283)	
Study 070		
FACTIVE 320 mg x 5 days	93.6 (247/264)	0.4 (-3.9, 4.6)
Amoxicillin/clavulanate 500 mg/125 mg tid x 7 days	93.2 (248/266)	
Study 212		
FACTIVE 320 mg x 5 days	88.2 (134/152)	3.1 (-4.7, 10.7)
Levofloxacin 500 mg x 7 days	85.1 (126/148)	

Community Acquired Pneumonia (CAP)

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults consisted of three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Pivotal study 011 compared a 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. The results of the clinical studies with a fixed 7-day duration are shown in Table 8:

Table 8. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7 Day Duration of Treatment

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
Study 011		
FACTIVE 320 mg x 7 days	88.7% (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg tid x 10 days	87.6% (99/113)	
Study 061		
FACTIVE 320 mg x 7 days	91.7%(154/168)	(86.1, 95.2)
Study 287		
FACTIVE 320 mg x 7 days	89.8% (132/147)	(84.9, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown

The combined bacterial eradication rates for patients treated with a fixed 7-day treatment regimen of FACTIVE are shown in Table 9:

Table 9. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
S. pneumoniae	68/77	88.3
M. pneumoniae	21/22	95.5
H. influenzae	30/35	85.7
C. pneumoniae	13/14	92.9
*K. pneumoniae**	11/13	84.6
M. catarrhalis	10/10	100

* Subjects with *Klebsiella pneumoniae* included in this table were from non-comparative studies 061 and 287. 10 of these subjects had mild disease, 2 had moderate disease, and 1 had severe disease. Both failures were in subjects with mild disease (one of these had a bacteriologic recurrence).

FACTIVE was also effective in the treatment of CAP due to PRSP (penicillin MIC of ≥2 μg/mL). Of 11 patients with PRSP treated for 7 days, 100% achieved clinical and bacteriological success at follow-up. Two of these subjects were classified as having severe disease and were bacteremic.

Cutaneous Manifestations (Rash)

In clinical trials of 6,775 patients, the incidence of rash was higher in patients receiving gemifloxacin than in those receiving comparator drugs (see **PRECAUTIONS** and **ADVERSE REACTIONS**). Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). (See Table 2).

To further characterize gemifloxacin-associated rash, a clinical pharmacology study was conducted. The study enrolled 1,011 healthy female volunteers less than 40 years of age. Subjects were randomized to receive either FACTIVE 320 mg po daily or ciprofloxacin 500 mg po twice daily for 10 days. The objective of the study was to assess the characteristics of rash. The majority of rashes in subjects receiving FACTIVE were maculopapular and of mild to moderate severity; 7% of the rashes were reported as severe, and severity appeared to correlate with the extent of the rash. In 68% of the subjects reporting a severe rash and approximately 25% of all those reporting rash, >60% of the body surface area was involved; the characteristics of the rash were otherwise indistinguishable from those subjects reporting a mild rash. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruption. There were no documented cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious cutaneous reactions.

The majority of rash events (81.9%) occurred on days 8 through 10 day of the planned 10 day course of gemifloxacin; 2.7% of rash events occurred within one day of the start of dosing. The median duration of rash was 6 days. The rash resolved without treatment in the majority of subjects. Approximately 19% received antihistamines and 5% received steroids, although the therapeutic benefit of these therapies is uncertain.

In the second part of this study after a 4 to 6 week wash out period, subjects developing a rash on gemifloxacin were treated with ciprofloxacin or placebo; 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. The characteristics of rash in subjects receiving ciprofloxacin following gemifloxacin were similar to those described in subjects who only received ciprofloxacin. The cross sensitization rate to other fluoroquinolones was not evaluated in this clinical study. There

was no evidence of sub-clinical sensitization to gemifloxacin (i.e. subjects who had not developed a rash to gemifloxacin in the first part of the study were not at higher risk of developing a rash to gemifloxacin with a second exposure).

There was no relationship between the incidence of rash and systemic exposure (Cmax and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Eighth Edition. Approved Standard NCCLS Document A2-A8, Vol. 23, No. 1, NCCLS Wayne, PA, January 2003.

Patient Information

This leaflet summarizes the most important information about FACTIVE. Read the Patient Information that comes with FACTIVE each time you get a new prescription. There may be new information. This leaflet does not list all benefits and risks of treatment and does not take the place of talking with your healthcare provider about your condition or your

treatment. FACTIVE can only be prescribed by a healthcare professional. If you would like more information, talk with your healthcare provider or pharmacist.

What is FACTIVE?
FACTIVE is an antibiotic. It is used to treat adults 18 years or older with bronchitis or pneumonia (lung infections) caused by certain bacteria (germs).

Sometimes, other germs called viruses infect the lungs. The common cold is a virus. FACTIVE, like other antibiotics, does not treat viruses.

FACTIVE tablets are white to off white and imprinted with GE 320 on both sides.

Who should not take FACTIVE?
- **Do not take FACTIVE if you are allergic to any of the ingredients in FACTIVE or to any antibiotic called a "quinolone" .** If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, stop taking FACTIVE and call your healthcare professional. The ingredients in FACTIVE are listed at the end of this leaflet. Ask your healthcare provider or pharmacist if you need a list of quinolones.

FACTIVE may not be right for you. Tell your healthcare provider if you:
- are pregnant, planning to become pregnant, or are breast feeding.. The effects of FACTIVE on unborn children and nursing infants are unknown.
- or any family members have a rare heart condition known as congenital prolongation of the QTc interval.
- have low potassium or magnesium levels.
- have a slow heart beat called bradycardia.
- have had a recent heart attack.
- have a history of convulsions.
- have kidney problems

FACTIVE has not been studied in children under the age of 18. Quinolones may cause joint problems (arthropathy) in children.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and dietary supplements. **Be sure to tell your healthcare provider if you take:**
- medicines for your heart rhythm called "antiarrhythmics"

- erythromycin
- medicines for your mental health called " antipsychotics" or "tricyclic antidepressants"
- medicines called "corticosteroids", taken by mouth or by injection
- medicines called diuretics such as furosemide and hydrochlorothiazide

How should I take FACTIVE?

- Take 1 FACTIVE tablet a day for 5 or 7 days, exactly as prescribed.
- Take FACTIVE at the same time each day.
- FACTIVE can be taken with or without food.
- Swallow the FACTIVE tablet whole, and drink plenty of fluids with it. Do not chew the FACTIVE tablet.
- If you miss a dose of FACTIVE, take it as soon as you remember. **Do not take more than 1 dose of FACTIVE in a day.**
- To make sure all bacteria are killed, take all the medicine that was prescribed for you even if you begin to feel better
- Call your healthcare provider if your condition does not improve while taking FACTIVE.

Do not take the following medicines within 3 hours before FACTIVE or 2 hours after FACTIVE. They may interfere with the absorption of FACTIVE and may prevent it from working properly:

- antacids that contain magnesium or aluminum
- ferrous sulfate (iron)
- multivitamin that contains zinc or other metals
- Videx® (didanosine)

FACTIVE should be taken at least 2 hours before sucralfate.

What are possible side effects of FACTIVE?

FACTIVE is generally well tolerated. The most common side effects with FACTIVE include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change in the way things taste in your mouth. If you get a rash while taking FACTIVE, stop FACTIVE, and call your healthcare provider right away. Do not drive or operate heavy machinery until you know how FACTIVE affects you. FACTIVE can make you dizzy.

FACTIVE and other quinolone antibiotics may cause the following serious side effects:

- a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and result in sudden death. You should call your healthcare provider right away if you have any symptoms of prolongation of the QTc interval including heart palpitations (a change in the way your heart beats) or fainting spells.

- central nervous system problems including body shakes (tremors), restless feeling, lightheaded feelings, confusion, and hallucinations (seeing or hearing things that are not there).
- tendon problems including tendonitis or rupture ("tears") of a tendon. If you experience pain, swelling, or rupture of a tendon, stop taking FACTIVE and call your healthcare professional.
- phototoxicity. This can make your skin sunburn easier. Do not use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear protective clothing if you must be out in the sun.

The most common side effects with FACTIVE include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change in the way things taste in your mouth.

These are not all the side effects you may experience with FACTIVE. If you get any side effects that concern you, call your healthcare provider.
General information about the safe and effective use of FACTIVE:
Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use FACTIVE for a condition for which it was not prescribed. Do not give FACTIVE to other people, even if they have the same symptoms that you have. It may harm them. **Keep FACTIVE and all medicines out of the reach of children.**

What are the ingredients in FACTIVE?
Active ingredient: gemifloxacin
Inactive Ingredients: crospovidone, hydroxypropyl methycellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.

DATE OF ISSUANCE MONTH YEAR

Rx only

LG Life Sciences, Ltd.
Seoul 150-721 KOREA

US005776944A

United States Patent [19]

Hong et al.

[11] Patent Number: 5,776,944

[45] Date of Patent: Jul. 7, 1998

[54] **7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROPLIDIN-1-YL)-1-CYCLOPROPYL-6-FLU ORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF**

[75] Inventors: **Chang Yong Hong; Young Kwan Kim; Se Ho Kim; Jay Hyok Chang; Hoon Choi; Do Hyun Nam; Ae Ri Kim; Jin Hwa Lee; Ki Sook Park**, all of Daejeon, Rep. of Korea

[73] Assignee: **LG Chemical Ltd.**, Seoul, Rep. of Korea

[21] Appl. No.: **825,992**

[22] Filed: **Apr. 4, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 490,978, Jun. 15, 1995, Pat. No. 5,633,262.

[30] **Foreign Application Priority Data**

Jun. 16, 1994	[KR]	Rep. of Korea	94-13604
Dec. 30, 1994	[KR]	Rep. of Korea	94-39915
Dec. 30, 1994	[KR]	Rep. of Korea	94-39930

[51] **Int. Cl.**[6] **A61K 31/435**; C07D 405/14

[52] **U.S. Cl.** **514/300**; 546/123

[58] **Field of Search** 514/300; 546/123

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0541086	5/1993	European Pat. Off. .
1-100165	4/1989	Japan .

OTHER PUBLICATIONS

Lesher et al., "1, 8-Naphthyridine Derivatives. A New Class of Chemotherapeutic Agents", *J. Med. Chem.*, vol. 5, pp. 1063–1065, 1962.

Koga et al., "Structure–Activity Relationships of Antibacterial 6,7– and 7,8–Disubstituted 1–Alkyl–1,4–dihydro–4–oixoquinoline–3–carboxylic Acids", *J. Med. Chem.*, vol. 23, pp. 1358–1363, 1980.

Wise et al., "In Vitro Activity of Bay 09867, a New Quinoline Derivative, Compared with Those of Other Antimicrobial Agents", *J. Antimicrob. Agents Chemother*, vol. 23, pp. 559–564, 1983.

Sato et al., "In Vitro and In Vivo Activity of DL–8280, a New Oxazine Derivative", *J. Antimicrob. Agents Chemother*, vol. 23, pp. 548–553, 1982.

Rosen et al., "Design, Synthesis, and Properties of (4S)–7–(4–Amino–2–substituted–pyrrolidin–1–yl) quinolone–3–carboxylic Acids", *J. Med. Chem.*, vol. 31, pp. 1598–1611, 1988.

Matsumoto et al., "AT–3295, a New Pyridonecarboxylic Acid Derivative with Potent Antibacterial Activity: Synthesis and Structure–activity Relationships", *Proceedings of the 14th International Congress of Chemotheraphy* pp. 1519–1520, 1985.

Cooper et al., "Preparation and in Vitro and in Vivo Evaluation of Quinolones with Selective Activity against Gram–Positive Organisms", *J. Med. Chem.*, vol. 35, pp. 1392–1398, 1992.

Domagala et al., "Synthesis and Biological Activity of 5–Amino–and 5–Hydroxyquinolones, and the Overwhelming Influence of the Remote N–Substituent in Determining the Structure–Activity Relationship", *J. Med. Chem.*, vol. 34, pp. 1142–1154, 1991.

Domagala et al., "1–Substituted, 7–[3–[Ethylamoni) methyl]–1–pyrrolidinyl]–6,8–difluoror–1, 4–dihydro–4–oxo–3–quinolinecarboxylic Acids. New Quantititative Structure–Activity Relationships at N for the Quinolone Antibacterials", *J. Med. Chem.*, vol. 31, pp. 991–1001,1988.

Bouzard et al., "Fluoronaphthyridines as Antibacterial Agents. 4. Synthesis and Structure–Activity Relationships of 5–Substituted–6–fluoro–7–(cycloalkylamino)–1, 4–dihydro–4–oxo–1,8–naphthyridine–3–carboxylic Acids", *J. Med. Chem.*, vol. 35, pp. 518–525, 1992.

Parikh et al., "Sulfur trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide", *JACS.*, vol. 89, pp. 5505–5507, 1967.

CA 114: 164195r, p. 775, 1991.

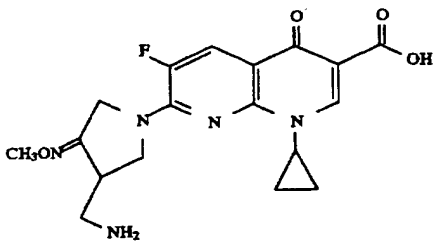
CA119:203318h, p. 884, 1993.

Primary Examiner—Joseph McKane

Attorney, Agent, or Firm—Banner & Witcoff, Ltd.

[57] **ABSTRACT**

The present invention relates to a novel quinolone compound having an excellent antibacterial activity. More specifically, the present invention relates to 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid represent by the following formula:



or its isomer.

16 Claims, 10 Drawing Sheets

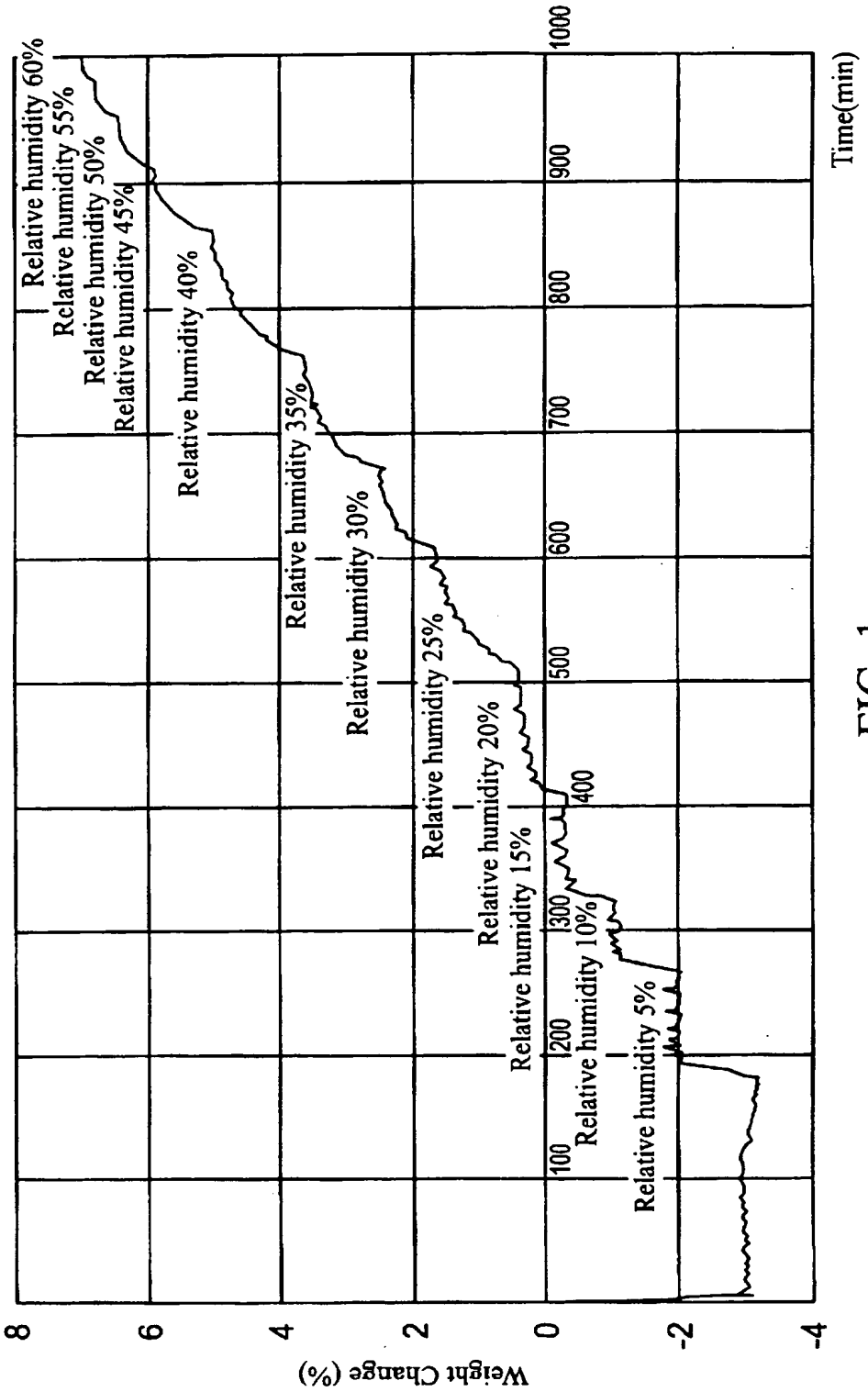

Relative humidity 60%
Relative humidity 55%
Relative humidity 50%
Relative humidity 45%
Relative humidity 40%
Relative humidity 35%
Relative humidity 30%
Relative humidity 25%
Relative humidity 20%
Relative humidity 15%
Relative humidity 10%
Relative humidity 5%
Weight Change (%)
8
6
4
2
0
-2
-4
100
200
300
400
500
600
700
800
900
1000
Time(min)

FIG. 1

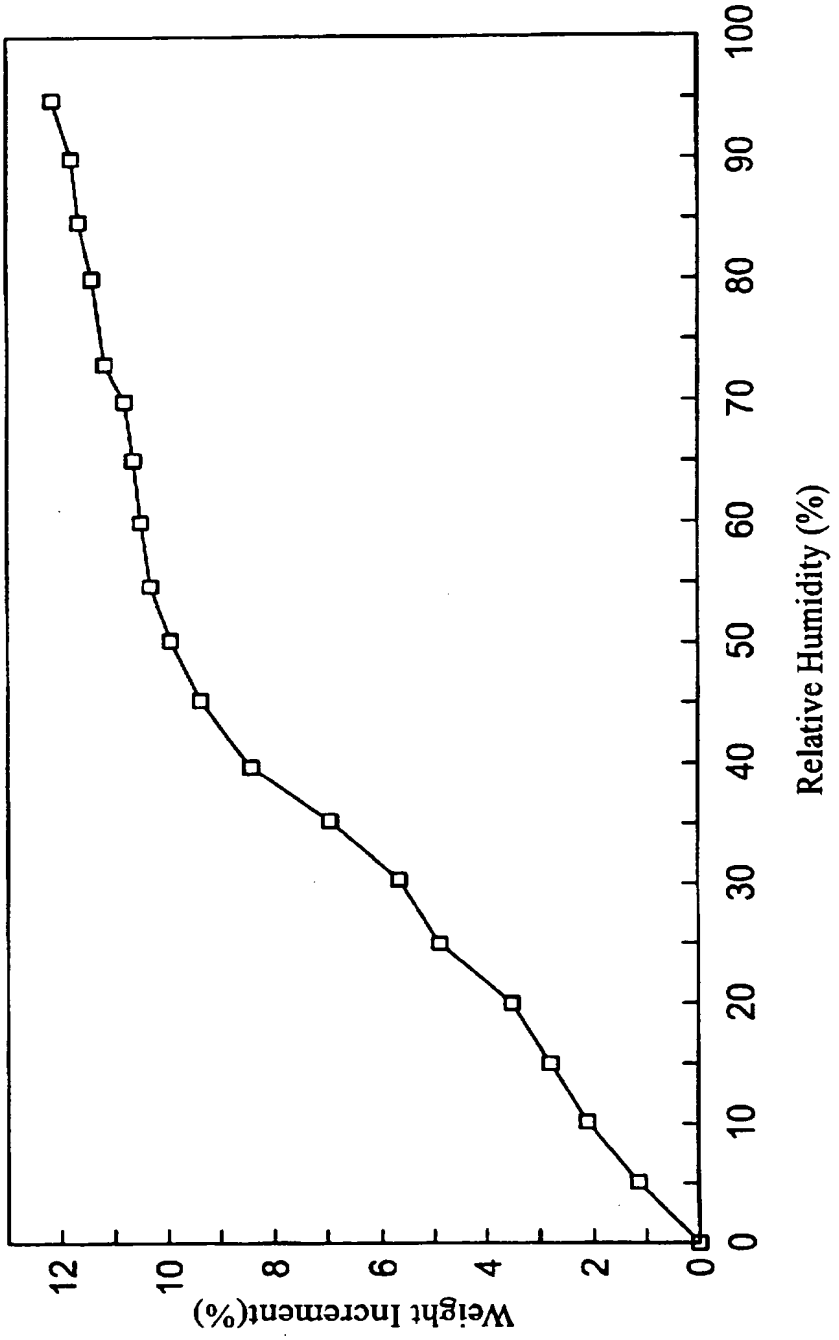

Weight Increment(%)
0
2
4
6
8
10
12
Relative Humidity (%)
0
10
20
30
40
50
60
70
80
90
100

FIG. 2

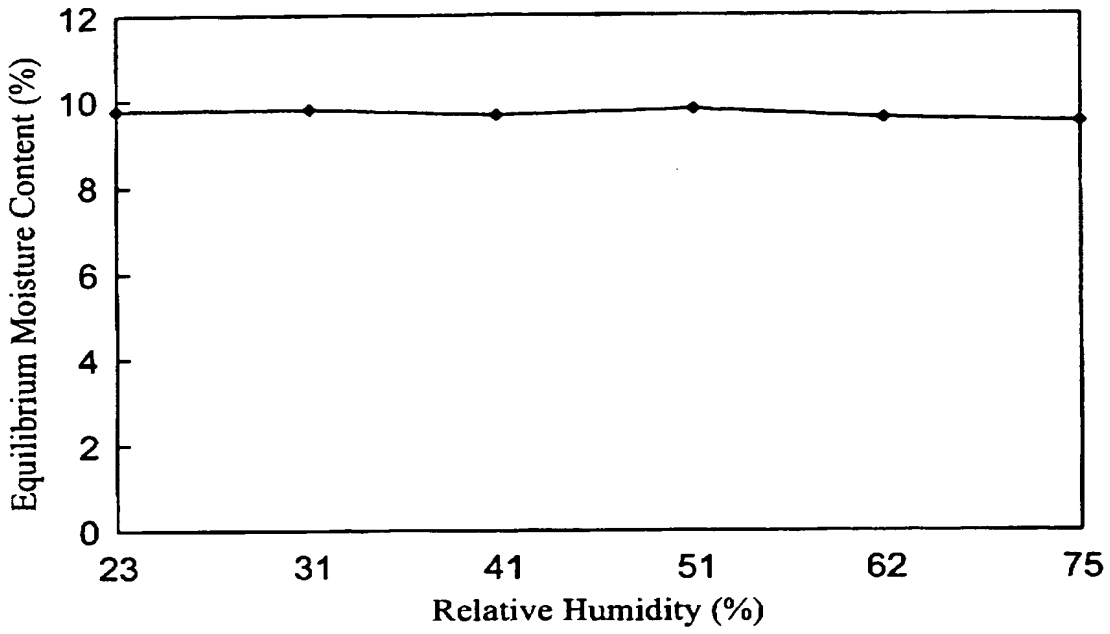

12
10
8
6
4
2
0
Equilibrium Moisture Content (%)
23
31
41
51
62
75
Relative Humidity (%)

FIG. 3

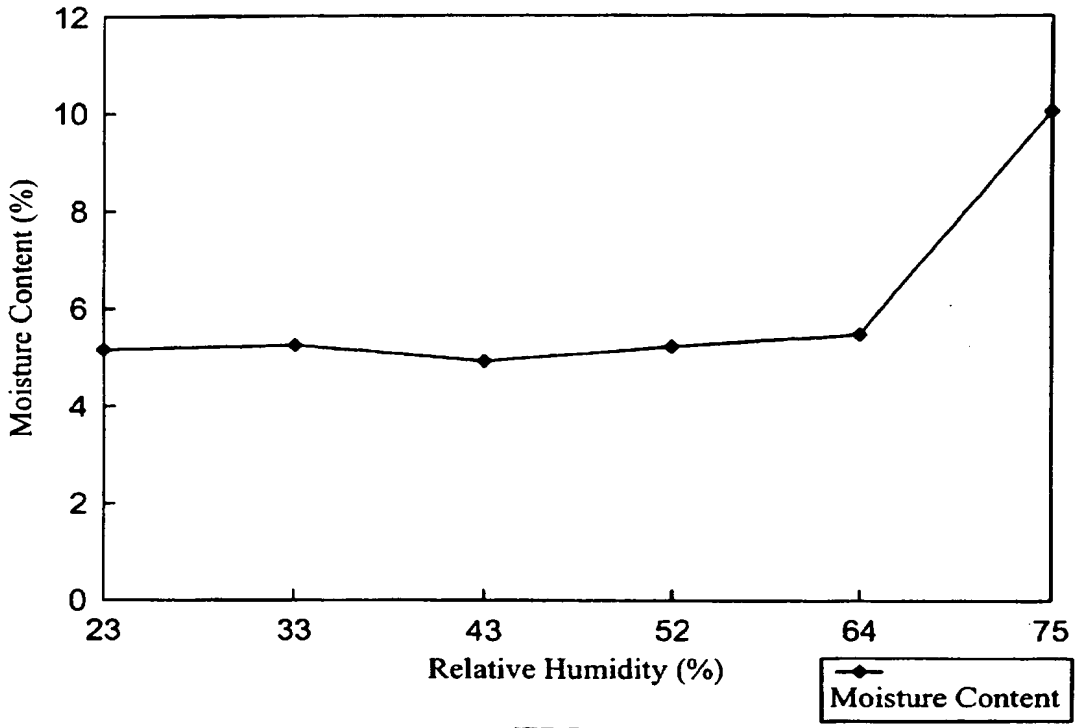

12
10
8
6
4
2
0
Moisture Content (%)
23
33
43
52
64
75
Relative Humidity (%)
Moisture Content

FIG. 4

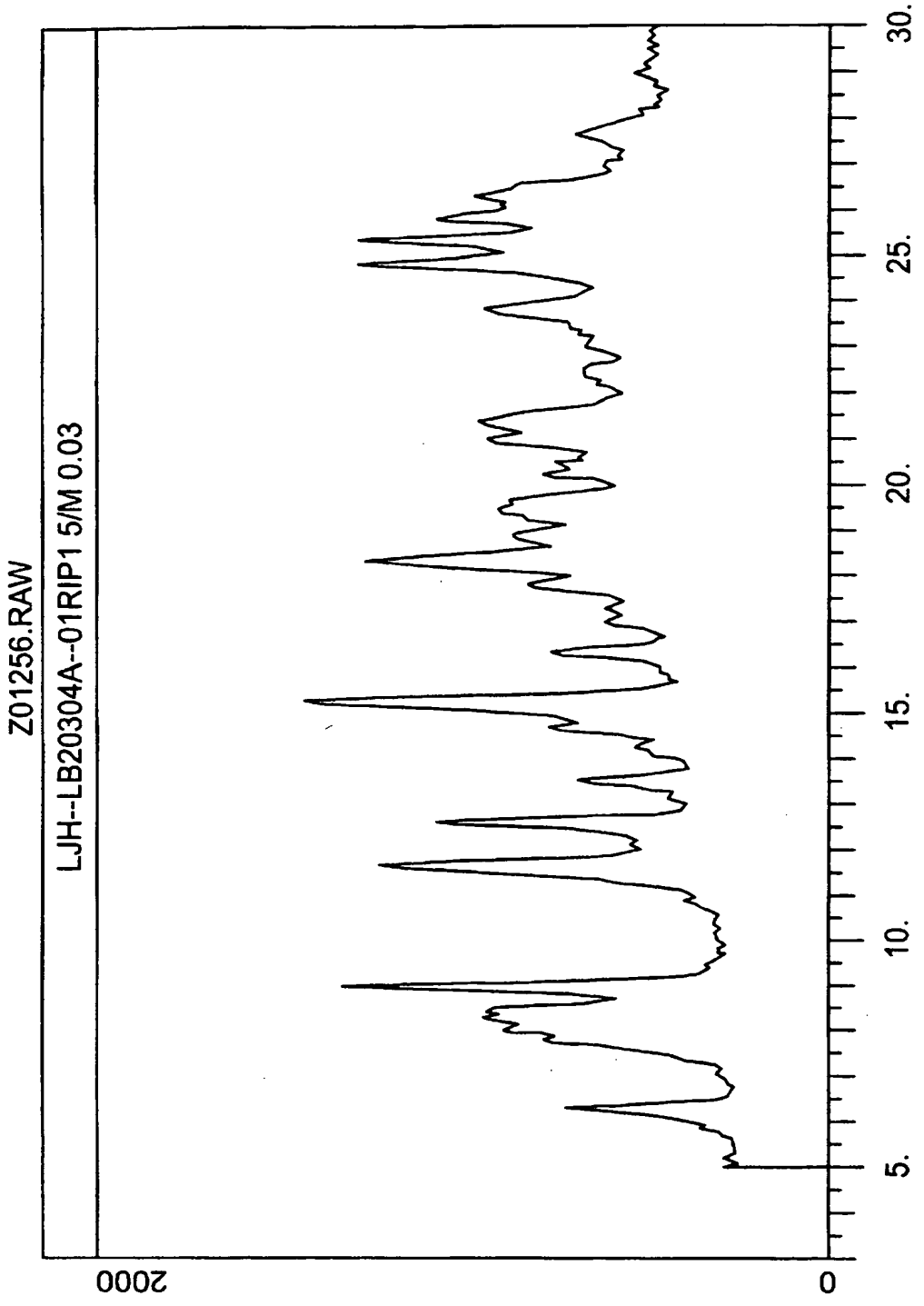


FIG. 5

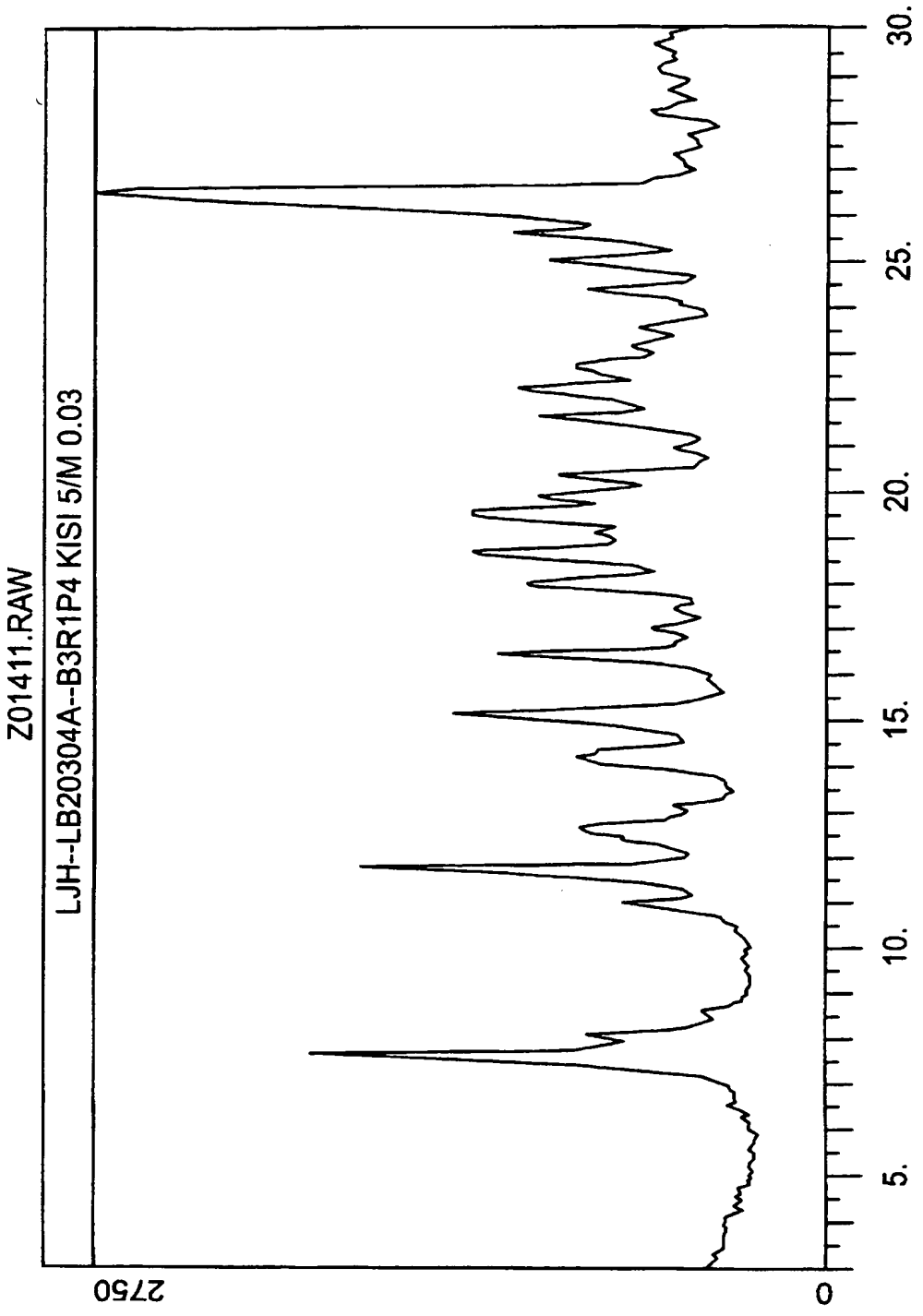

Z01411.RAW
LJH--LB20304A--B3R1P4 KISI 5/M 0.03
2750
0
5.
10.
15.
20.
25.
30.

FIG. 6

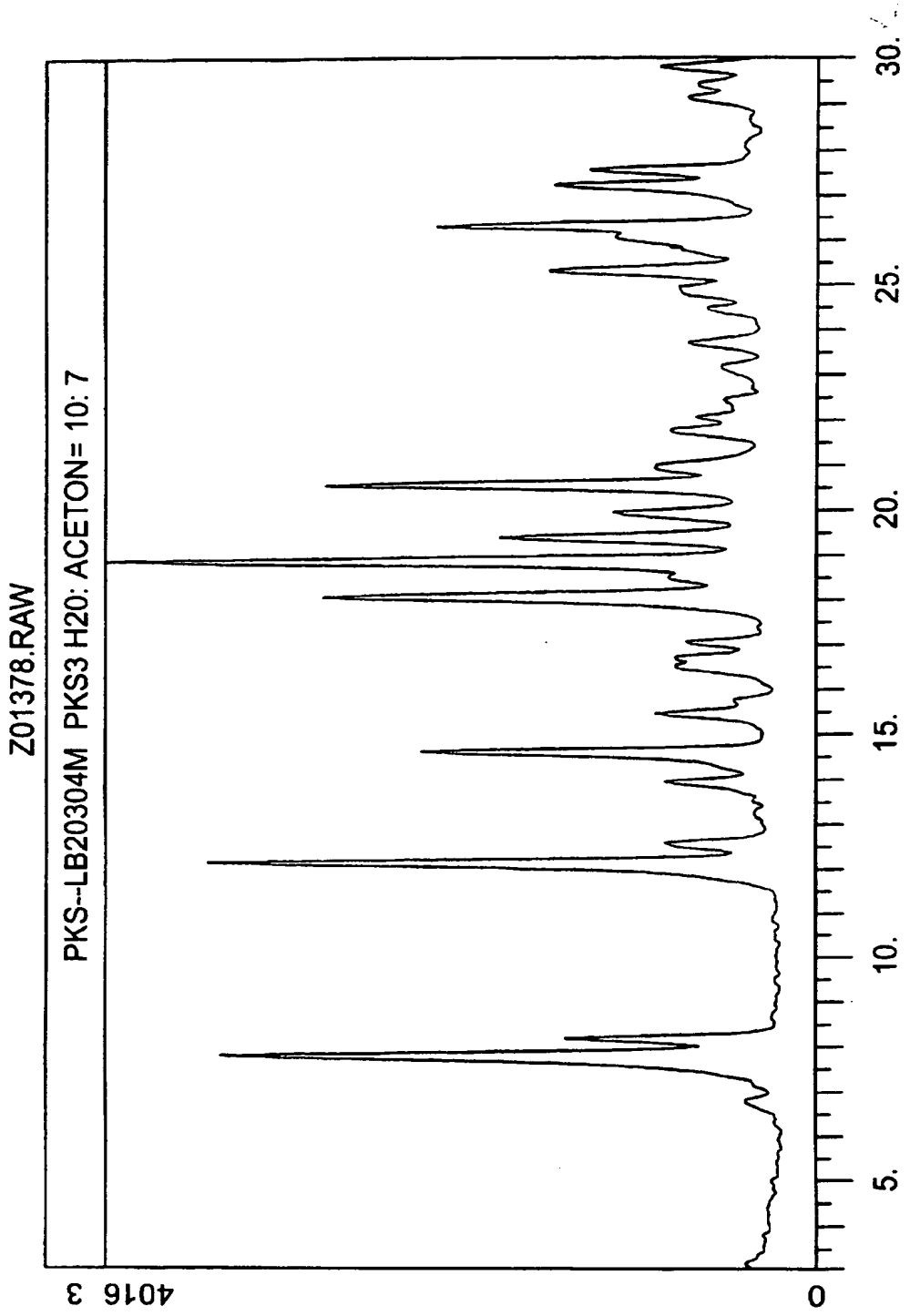

Z01378.RAW
PKS--LB20304M PKS3 H20: ACETON= 10: 7
4016 3
0
5.
10.
15.
20.
25.
30.

FIG. 7

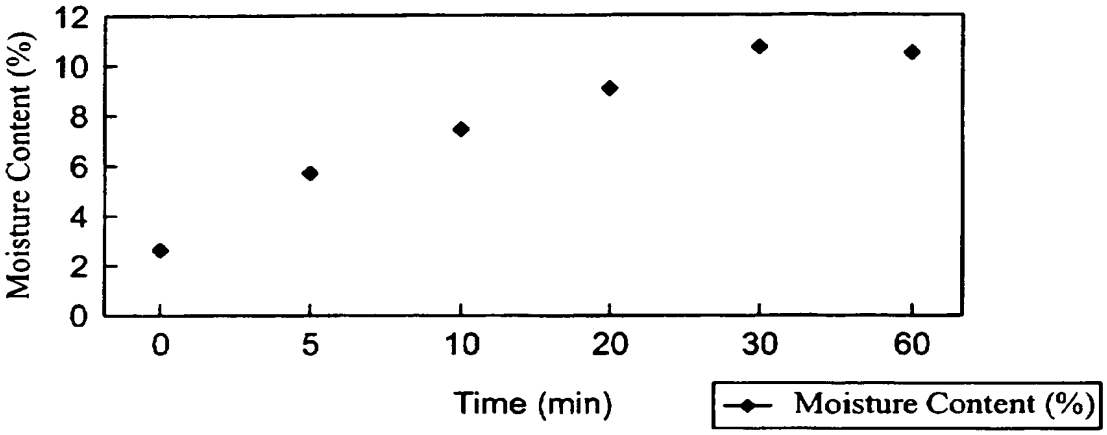

Moisture Content (%)
12
10
8
6
4
2
0
0
5
10
20
30
60
Time (min)
Moisture Content (%)

FIG. 8

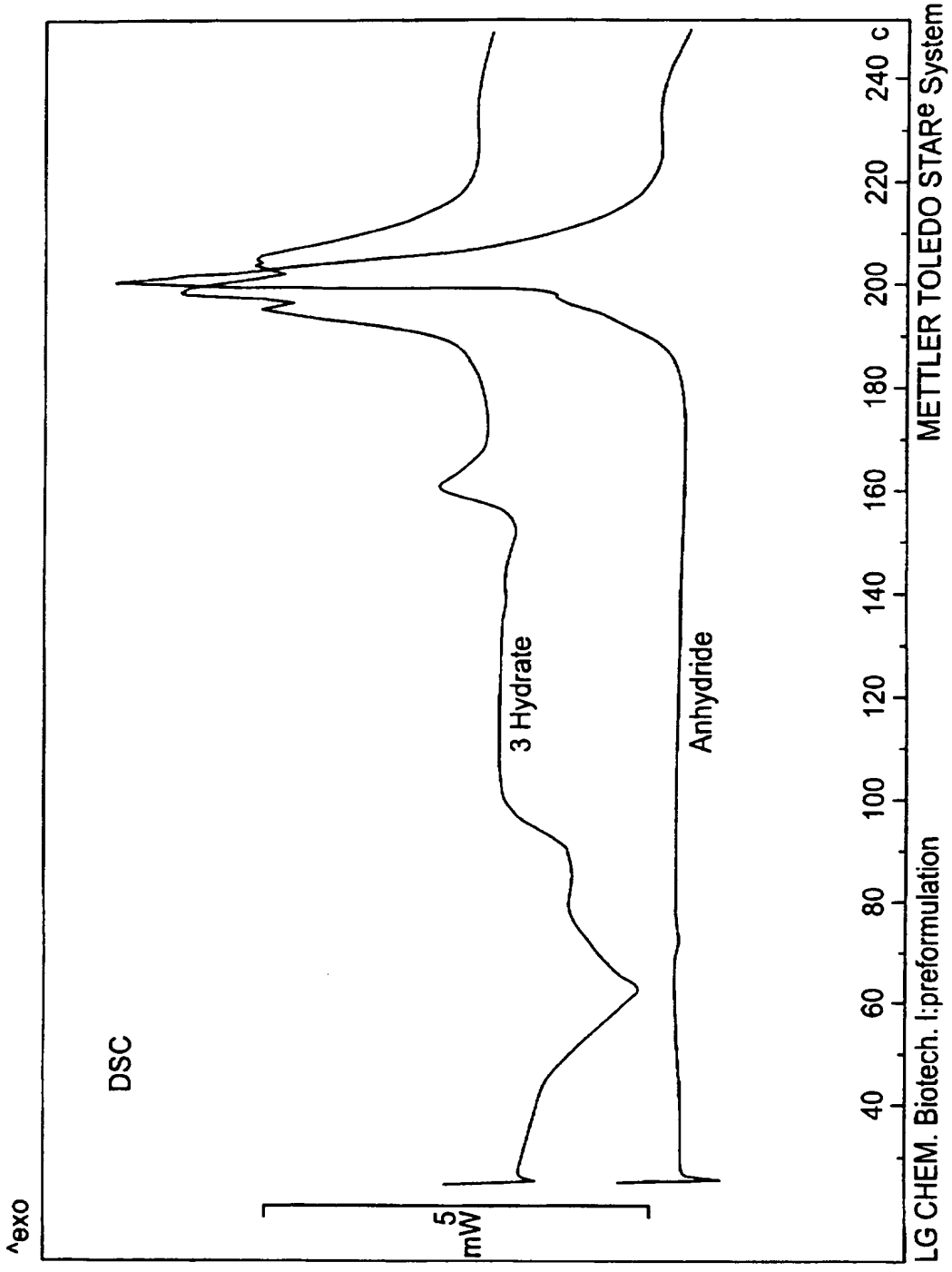

^exo
DSC
5
mW
3 Hydrate
Anhydride
40
60
80
100
120
140
160
180
200
220
240 c
LG CHEM. Biotech. I:preformulation
METTLER TOLEDO STARe System

FIG. 9

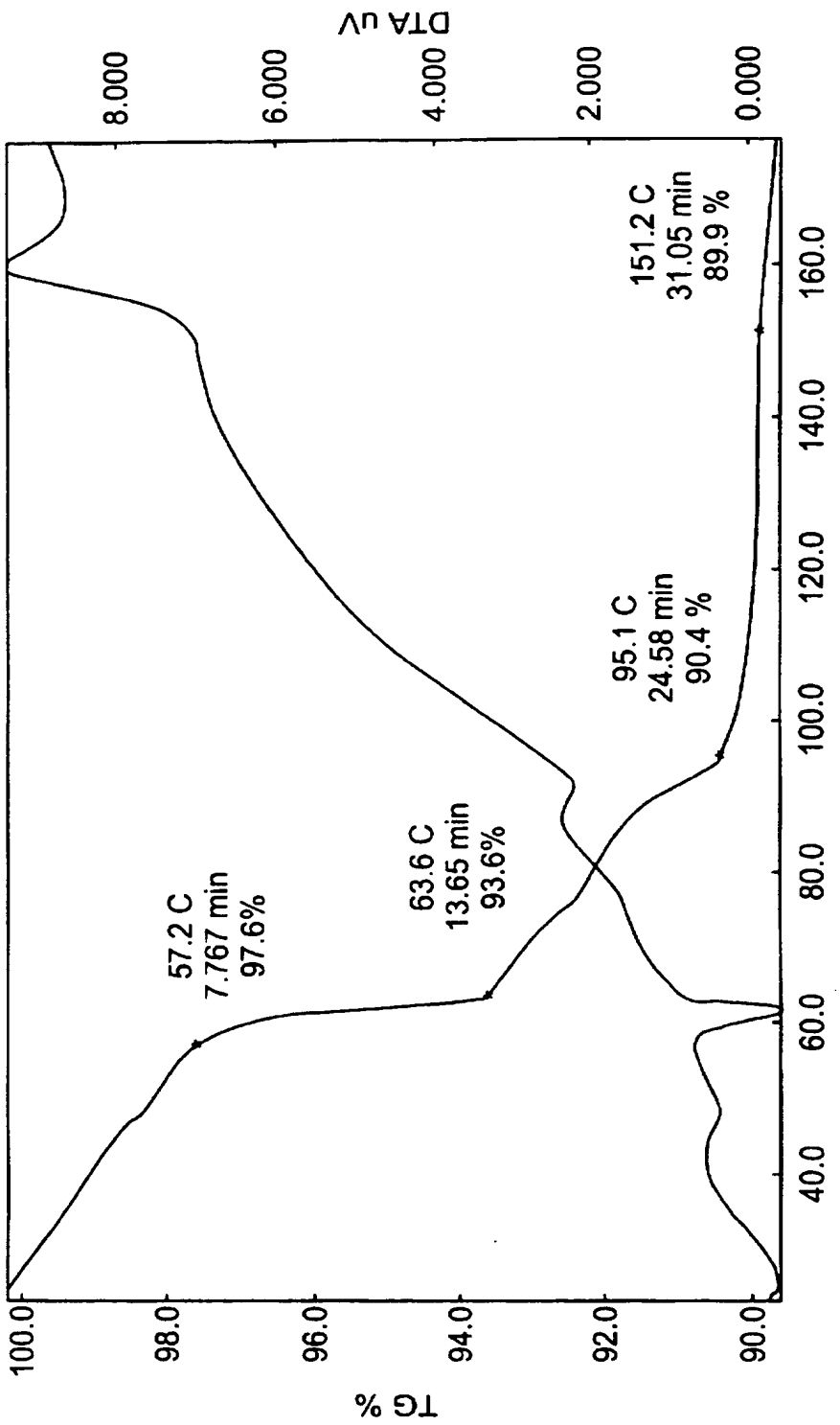

DTA uV
8.000
6.000
4.000
2.000
0.000
TG %
100.0
98.0
96.0
94.0
92.0
90.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
Temp. C
57.2 C
7.767 min
97.6%
63.6 C
13.65 min
93.6%
95.1 C
24.58 min
90.4 %
151.2 C
31.05 min
89.9 %

FIG. 10

7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROPLIDIN-1-YL)-1-CYCLOPROPYL-6-FLU ORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF

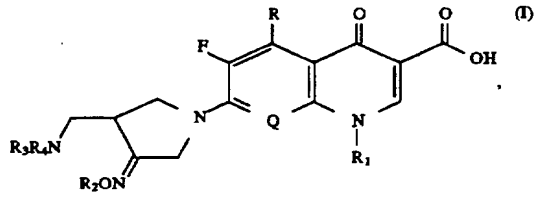
CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of U.S. patent applicaton Ser. No. 08/490,978 filed Jun. 15, 1995, now U.S. Pat. No. 5,633,262.

BACKGROUND OF INVENTION

1. Field of Invention

The present invention relates to a novel quinoline (naphthyridine) carboxylic acid derivative having an excellent antibacterial activity. More specifically, the present invention relates to a novel quinoline(naphthyridine) carboxylic acid derivative represented by the following formula (I), which has an 4-aminomethyl-3-oximepyrrolidine substituent on 7-position of the quinolone nucleus and shows a superior antibacterial activity in contrast to the known quinolone antibacterial agents and also has a broad antibacterial spectrum and a highly improved pharmacokinetic property:



and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

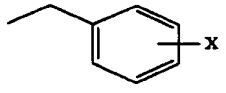
Q represents C—H, C—F, C—Cl, C—OH, C—CH_3, C—O—CH_3 or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1–C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3–C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

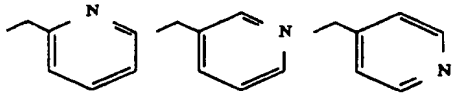
b) a group of the following formula (1),



(1)

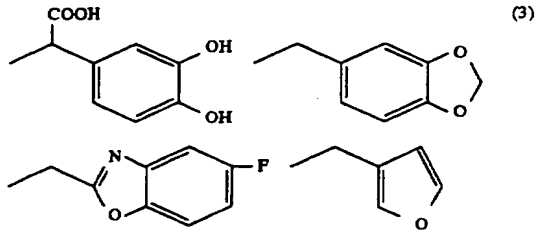
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1–C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



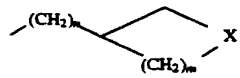
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

e) a group of the following formula (4),



(4)

wherein n denotes 0 or 1, m denotes 0, 1 or 2, and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1–C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring.

The present invention also relates to a process for preparing the compound of formula (I), as defined above, and an antibacterial composition comprising the compound of formula (I) as an active component.

2. Background Art

Since in 1962 nalidixic acid was first introduced as an agent for treating urinary tract infection (see, G. Y. Lesher, et al., J. Med. Chem. 5, 1063–1065 (1962)), numerous quinoline carboxylic acid antibacterial agents, including oxolinic acid, rosoxacin, pipemidic acid, etc., have been developed. However, these early-stage antibaterial agents have a little activity against gram-positive bacterial strains and thus have been used only against gram-negative strains.

Recently, norfloxacin which is the quinolone compound having a fluorine on 6-position has been newly developed (see, H. Koga, et al., J. Med. Chem., 23, 1358–1363 (1980)), and thereafter an extensive study to develop various quinolone antibacterial compounds has been conducted. However, since norfloxacin has a weak antibacterial activity against gram-positive strains and shows poor distribution and absorption in living body, it has been used only for treatment of diseases including urinary tract infections, gastro-intestinal infections, sexually transmitted diseases and the like. Thereafter, ciprofloxacin (see, R. Wise, et al., J. Antimicrob. Agents Chemother., 23, 559 (1983)), ofloxacin (see, K. Sata, et al., Antimicrob. Agents Chemother., 22, 543 (1982)) and the like have been developed. These antibacterial agents have a superior and broad antibacterial activity in comparison with the early-stage antibacterial compounds, and therefore, have been widely and practically used for treatment of diseases in clinical field.

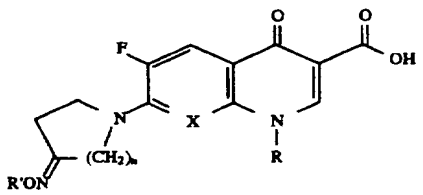
The compounds in use or under clinical test include mainly the derivatives having a piperazine substituent on 7-position of the quinolone nucleus as in ciprofloxacin or ofloxacin. However, as a result of the study to develop quinolone compounds having a more potent and broad antibacterial activity it has been disclosed that a compound having an 3-amino or 3-aminomethylpyrrolidine group introduced into 7-position has an increased activity against gram-positive strains, in comparison with the compounds having 7-piperazine group, while maintaining a potent activity against gram-negative strains. However, unfortunately, the compounds having pyrrolidine substituent have a low

solubility in water in comparison with the compounds having piperazine substituent, and thus their in-vivo antibacterial activity is not so high as the in-vitro activity. Accordingly, numerous study has been continuously conducted to improve the disadvantage of the compounds having pyrrolidine substituent, that is, to increase the solubility in water and to improve the pharmacokinetic property.

As a result, many reports of such study have been made. For example, it has been disclosed that ((2S, 4S)-4-amino-2-methylpyrrolidinyl)naphthyridine derivatives (see, Rosen, T., Chu, D. T. W. etc. J. Med. Chem. 1988, 31, 1598–1611) or (trans-3-amino-4-methylpyrrolidinyl)naphthyridine derivatives (see, Matsumoto, J. et al., Proceedings of the 14th International Congress of Chemotherapy; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, 1905; pp 1519–1520) shows a 20 to 40 times increase in water-solubility, an increased bioavailability and an improved pharmacolinetic property, in comparison with the compounds having no methyl group, with a similar in-vitro antibacterial activity.

In addition, an attempt to improve the disadvantage of the prior quinolone compounds including a relatively low antibacterial activity against gram-positive strains, a low water-solubility and a poor pharmacokinetic property has been made by introducing different functional groups, instead of amino group, into the pyrrolidine or piperazine moiety. As one of such attempt, some compounds having an oxime group introduced into the 7-amine moiety of quinolone compounds have been reported. For example, the researchers of Abbott have reported in a scientific journal, J. Med. Chem., 1992, 35, 1392–1398, that the quinolone compound having the following general formula [A] wherein 3-oxime (or methyloxime)pyrrolidine group or 4-oxime(or methyloxime)piperidine group is substituted on 7-position of quinolone nucleus exhibits a good antibacterial activity against gram-positive strains:

[A]



in which

R represents cyclopropyl or 2,4-difluorophenyl;

R' represents hydrogen or methyl;

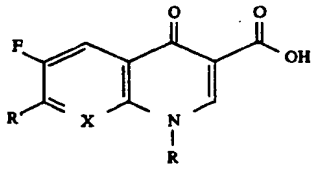
X represents C—H, C—F or N; and

n denotes 1 or 2.

The compound [A] has some disadvantages that it shows a good antibacterial activity against gram-positive strains but a relatively weak activity against gram-negative strains, and also has a relatively low antibacterial activity in in-vivo test.

In addition, Japanese Laid-open Patent Publication No. (Hei) 01-100165 (1989) discloses the compound having the following general formula [B]:

[B]



in which

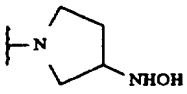
R represents cyclopropyl, 2,4-difluorophenyl or 4-hydroxy-phenyl;

X represents C—H, C—F or C—Cl; and

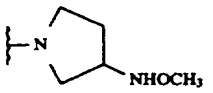
R' represents oxime or hydroxyaminopyrrolidine-derived substituent.

Specifically, in said Japanese laid-open publication the oxime or hydroxyaminopyrrolidine-derived groups as R' substituent are very broadly disclosed. However, only the 3-hydroxyaminopyrrolidine [the following formula (a)], 3-methoxyaminopyrrolidine [the following formula (b)], 3-amino-4-methoxyaminopyrrolidine [the following formula (c)], 3-oximepyrrolidine [the following formula (d)] and 3-methyloximepyrrolidine [the following formula (e)] groups are specifically exemplified but the pyrrolidine substituent having both 3-oxime and 4-aminomethyl groups has never been specifically mentioned.

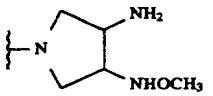
[a]



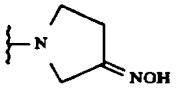
[b]



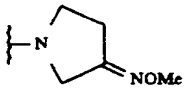
[c]



[d]

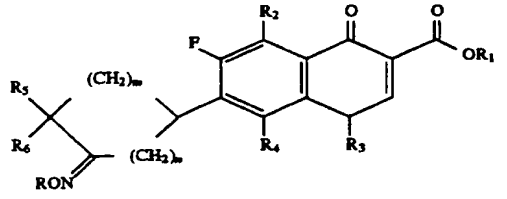


[e]



Further, European Early Patent Publication No. 0 541 086 discloses the quinolone compound having the following general formula [C]:

[C]



in which

R and R_1 independently of one another represent hydrogen or C_1–C_5 alkyl;

R_2 represents hydrogen, amino, fluoro or hydroxy;

R_3 represents C_3–C_7 cycloalkyl;

R_4 represents methoxy or fluoro;

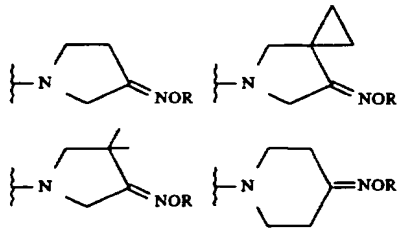
R_5 and R_6 can be identical with or different from each other and independently of one another represent hydrogen or alkyl, or

R_5 and R_6 together can form C_3–C_5 cycloalkyl;

m denotes 0 or 1; and

n denotes an integer of 1 to 3.

Among the compounds [C] disclosed in said European early patent publication the typical substituent on 7-position of quinolone nucleus is a group having the following structure:



However, the compound of formula [C] does not include any compound having both oxime group and aminomethyl group on 7-position, and therefore, is different from the compound of the present invention.

The common characteristic feature of the known oxime or hydroxyamine-derived compounds as mentioned above is that they exhibit a good activity against gram-positive strains including MRSA (Methicillin Resistant *Staphylococcus aureus*) strains in comparison with the early developed quinolone compounds but show a weak activity against gram-negative strains in comparison with the antibacterial agents including ofloxacin or ciprofloxacin. Therefore, it can be said that their antibacterial spectrum may be narrower than that of the known ofloxacin or ciprofloxacin antibacterial compound.

Thus, on the basis of prior art as mentioned above the present inventors have extensively studied to develop the novel oxime-aminomethyl compound, which shows a potent antibacterial activity against broad spectrum pathogenic strains including resistant strains and also exhibits more improved pharmacokinetic properties and high absorption in living body, by introducing various substituted pyrrolidine groups into 7-position of quinoline nucleus and determining pharmacological activities of the resulting compounds. As a result, we have identified that the quinolone compounds having the general formula (I), as defined above, wherein 4-aminomethyl-3-(optionally substituted)oxime-pyrrolidine group is introduced into 7-position of quinoline nucleus can satisfy such purpose, and thus completed the present invention.

Therefore, it is an object of the present invention to provide a novel quinoline(naphthyridine) carboxylic acid derivative of formula (I), as defined above, which shows a potent antibacterial activity against broad pathogenic strains including both gram-positive and gram-negative strains and also has a good pharmacokinetic property.

It is another object of the present invention to provide a process for preparing the novel quinoline(naphthyridine) carboxylic acid derivative of formula (I).

It is a further object of the present invention to provide an antibacterial composition comprising the novel quinoline (naphthyridine)carboxylic acid derivative of formula (I) as an active component.

BRIEF DESCRIPTION OF THE DRAWINGS

For a thorough understanding of the nature and objects of the invention, reference should be made to the following detailed description taken in connection with the accompanying drawings in which

FIG. 1 represents the moisture adsorption velocity profile of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate at 25° C.;

FIG. 2 represents the isothermal moisture adsorption profile of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate at 25° C.;

FIG. 3 represents the equilibrium moisture content of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate·3 hydrate at a relative humidity of 23 to 75%;

FIG. 4 represents test result on moisture adsorption of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate·1.5 hydrate;

FIG. 5 represents the powder X-ray diffraction pattern of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate anhydride;

FIG. 6 represents the powder X-ray diffraction pattern of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate·3 hydrate;

FIG. 7 represents the powder X-ray diffraction pattern of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate·1.5 hydrate;

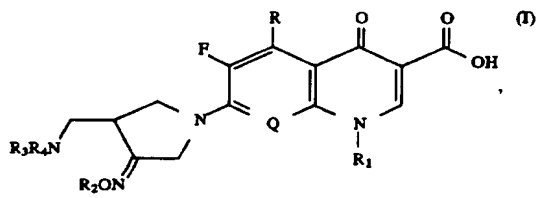
FIG. 8 represents the variation in moisture content with elapsed time of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclocropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate anhydride taken after 0, 5, 10, 20, 30, and 60 minutes, respectively, from the initial point while being passed through with humidified nitrogen;

FIG. 9 represents the results of Differential Scanning Calorimetry on 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate anhydride and 3 hydrate;

FIG. 10 represents the results of thermogravimetric analysis on 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate·3 hydrate.

DISCLOSURE OF INVENTION

In one aspect, the present invention relates to a novel quinoline(naphthyridine) carboxylic acid derivative having the following formula (I):



(I)

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

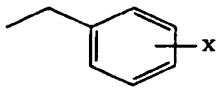
Q represents C—H, C—F, C—Cl, C—OH, C—CH_3, C—O—CH_3 or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1–C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3–C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

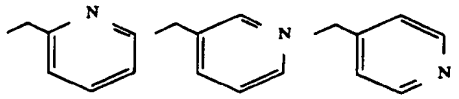
b) a group of the following formula (1),



(1)

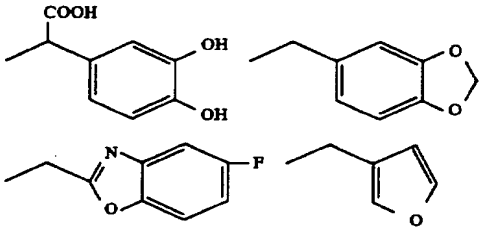
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1–C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



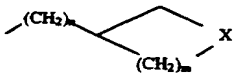
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

e) a group of the following formula (4),



(4)

wherein n denotes 0 or 1, m denotes 0, 1 or 2, and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1–C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring.

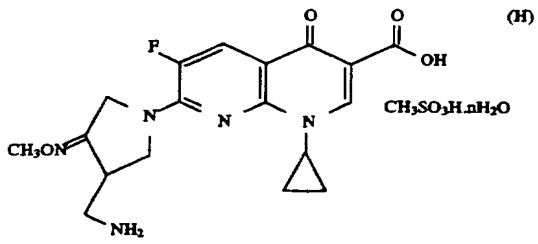
Among the compound of formula (I), as defined above, having a superior antibacterial activity, a broad antibacterial spectrum and an excellent pharmacokinetic property, the preferred compounds include those wherein Q represents C—H, C—F, C—Cl, C-OMe or N, R represents hydrogen or amino, R_1 represents cyclopropyl or 2,4-difluorophenyl, R_2 represents hydrogen, methyl, ethyl, isopropyl, t-butyl, phenyl, propargyl, homopropargyl, 2-fluoroethyl, benzyl, 2-fluorobenzyl or 2-cyanobenzyl, and R_3 and R_4 represent hydrogen.

More preferred compounds of formula (I) include those wherein Q represents C—H, C—Cl, C—F or N, R represents hydrogen or amino, R_1 represents cyclopropyl, R_2 represents methyl, t-butyl, homopropargyl, 2-fluoroethyl, henzyl or 2-fluorobenzyl, and R_3 and R_4 represent hydrogen.

In the pyrrolidine moiety of the compound of formula (I) the 4-carbon atom on which aminomethyl group is substituted is an asymmetric carbon atom and thus can be present in the form of R or S or a mixture of R abd S. In addition, due to the presence of (optionally substituted) oxime group on 3-position of pyrrolidine moiety the compound of formula (I) can be present in the form of syn- and anti-isomers depending on their geometric structure. Thus, the present invention also includes all of those geometric isomers and their mixtures.

The compound of formula (I) according to the present invention can form a pharmaceutically acceptable non-toxic salt. Such salt includes a salt with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, etc., a salt with organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid or with sulfonic acids such as methanesulfonic acid, paratoluenesulfonic acid, etc., and a salt with other acids which are generally known and conventionally used in the technical field of quinolone-based compounds. These acid-addition salts can be prepared according to a conventional conversion method.

Particularly, the present invention relates to the 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and its hydrate represented by the following formula (H),



(H)

in which n denotes 0, 1, 1.5, 2, 2.5, 3, 3.5 or 4, having an improved bioavailability.

The methanesulfonate and its hydrate as defined above exhibit the same potent antibacterial activity as the free form, also have desirable physicochemical properties such as excellent solubility, constant moisture content, etc. regardless of the ambient relative humidity.

Generally, conversion of a pharmacologically active compound into a salt form induces a change in the compound's physicochemical properties such as solubility, absorption velocity, etc. Therefore, study about an effective salt form for developing a successful new medicine has been conventionally made. Pharmaceutically more desirable crystal form may be selected by studying whether or not any pseudopolymorph can be produced and its physicochemical properties (see, Remington's Pharmaceutics, Chapter 75 Preformulation; Byrn, S. R. Solid Chemistry of Drugs, Academic Press, New York, 1982). The hydrate, one such pseudopolymorph, has water molecules inside the crystal, and thus has a crystalline structure different from that of the anhydride, as can be verified from their respective X-ray diffraction patterns. A pseudopolymorph differs from the original compound not in its chemical properties, such as pharmacological activity, but in its physical properties, such as crystallinity, hygroscopicity, melting point, solubility, solubilizing velocity, etc. So, the pseudopolymorph has been recognized as pharmaceutically important (see, Morris, K. P. et al., Int. J. Pharm., 108, 15–206 (1994)).

In the process of identifying the physicochemical properties of methanesulfonate, the salt has been found to exist as a stable hydrate when the number of water molecules

contained in one molecule varies within a specific range. Here, stability does not mean chemical stability but the difficulty of removing water molecules. That is, a stable hydrate neither loses the water molecules contained therein nor absorbs moisture over a wide range of ambient relative humidity. In contrast, moisture absorption by the anhydride varies greatly with the ambient relative humidity. As a result of experiments carried out by the present inventors, 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate has been shown to exist as a stable hydrate for values of the hydration number n equal only to 1, 1.5, 2, 2.5, 3, 3.5 or 4. Among these, 3 is preferred, since the change of moisture content is lowest at that hydration number.

The moisture content of the hydrate varies with the hydration number (n) of the hydrated molecule. Since the molecular weight of 7-(4-amino-methyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate is 485.5, the moisture content of the hydrate for n equal to 1, 1.5, 2, 2.5, 3, 3.5 or 4 is calculated to be 3.6%, 5%, 6.9%, 8.5%, 10.0%, 11.5% or 12.9%, respectively. However, the actual moisture content may differ from the calculated moisture content depending on differences in recrystallization conditions, drying conditions, etc. The range of the actual moisture content for each hydration number is shown in the following Table A.

TABLE A

Moisture Content according to Hydration Number

Hydration Number (n)	Moisture Content (%)
1	2–4
1.5	4–6
2	6–8
2.5	8–9
3	9–11
3.5	11–12
4	12–13

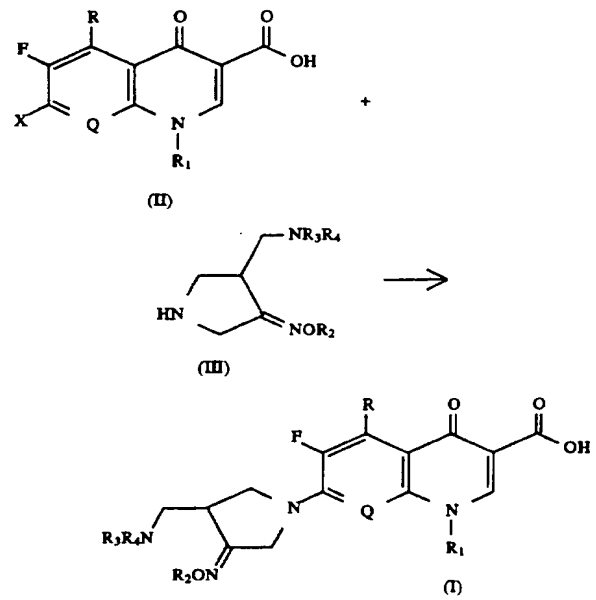
If two or more hydrates having different moisture contents are mixed together, mixtures having a new moisture content by weight, for example, a mixture of 1 hydrate and 1.5 hydrate having a moisture content of 2 to 6%; a mixture of 1.5 hydrate and 2 hydrate having a moisture content of 4 to 8%; a mixture of 2 and hydrate and 2.5 hydrate having a moisture content of 6 to 9%; a mixture of 2.5 hydrate and 3 hydrate having a moisture content of 8 to 11%; a mixture of 3 hydrate and 3.5 hydrate having a moisture content of 9 to 12%; or a mixture of 3.5 hydrate and 4 hydrate having a moisture content of 11 to 13%, can be obtained.

It has also been found that the relative humidity range at which the moisture content of each hydrate can be maintained constant differ from each other. That is, although the 3 hydrate has a constant moisture content at a relative humidity of 23 to 1.5 hydrate is constant at a relative humidity of 23 to 64% only (see, FIGS. 3 and 4).

In the second aspect, the present invention also relates to a process for preparing the novel compound of formula (I).

According to the present invention, the compound of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) or a salt thereof, as shown in the following reaction scheme 1.

Reaction Scheme 1



In the above scheme,

R, R_1, R_2, R_3, R_4 and Q are defined as previously described; and

X represents a halogen atom, preferably chlorine, bromine or fluorine.

According to the above reaction scheme 1, the compound of formula (I) according to the present invention can be prepared by stirring the compound of formula (II) and the compound of formula (III) in the presence of a solvent for 1 to 20 hours at the temperature between room temperature and 200° C. with the addition of a suitable base. In this reaction, the compound of formula (III) can be used in the form of a free compound or a salt with an acid such as hydrochloric acid, hydrobromic acid or trifluoroacetic acid.

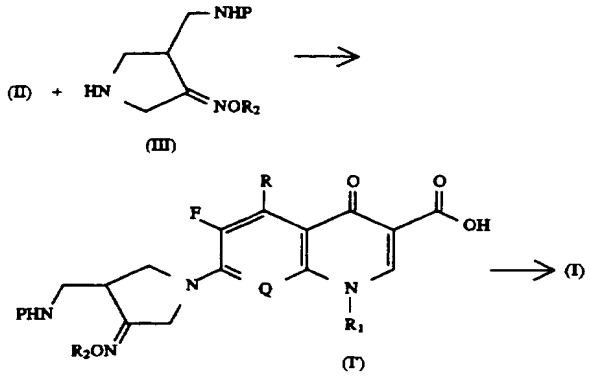
As the solvent for the above reaction, any solvent which does not adversely affect the reaction can be used. Preferably, acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO) pyridine, hexamethylphosphoramide (HMPA), N-methylpyrrolidinone, ethanol, and aqueous mixtures thereof can be used.

This reaction is generally conducted in the presence of an acid acceptor. In this case, to increase the reaction efficiency of the relatively expensive starting material (II) the reactant (III) is used in an excessive amount, for example, an equimolar amount to 10 times molar amount, preferably an equimolar amount to 5 times molar amount, with respect to the starting material (II). When the reactant (III) is used in an excessive amount, the unreacted compound of formula (III) which is retained after the reaction can be recoverd and reused in another reaction. The acid acceptor which can be preferably used in this reaction includes inorganic bases such as sodium hydrogen carbonate, potassium carbonate, etc., and organic bases such as triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0] undec-7-ene(DBU), 1,4-diazabicyclo[2.2.2] octane (DABCO), etc.

The compound of formula (I) according to the present invention can also prepared by a method depicted in the

following reaction scheme 2, in which a protecing group P is introduced into one of R_3 and R_4 of the compound of formula (III) wherein R_3 and R_4 are hydrogen to prepare the compound of formula (III') wherein the amino group is protected with P, the protected compound of formula (III') is reacted with the compound of formula (II) under the same condition as in the reaction scheme 1, and then the resulting compound of formula (I') is deprotected by removing the protecting group P to form the desired compound of formula (I).

Reaction Scheme 2



In the above reaction scheme,

R, R_1, R_2 and Q are defined as previously described; and P represents an amino-protecting group.

In the reaction of the above reaction scheme 2, the compound of formula (III') can be used in the form of a free compound or a salt with hydrochloric acid, hydrobromic acid or trifluoroacetic acid, as in the compound of formula (III) used in the reaction scheme 1.

Any protecting group which is conventionally used in the field of organic chemistry and can be readily removed after the reaction without decomposition of the structure of the desired compound can be used as the suitable amino-protecting group P in the compound of formula (III'). The specific example of protecting groups which can be used for this purpose includes formyl, acetyl, trifluoroacetyl, benzoyl, para-toluenesulfonyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, beta-iodoethoxycarbonyl, benzyl, para-methoxybenzyl, trityl, tetrahydropyranyl, para-nitrobenzoyl, etc.

After the reaction is completed, the amino-protecting group present in the resulting compound of formula (I') can be removed by hydrolysis, solvolysis or reduction depending on properties of the relevant protecting group. For example, the compound of formula (II) is treated in a solvent in the presence or absence of an acid or base at the temperature of 0° to 130° C. to remove the protecting group. As the acid which can be used for this purpose, an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc., an organic acid such as acetic acid, trifluoroacetic acid, formic acid, toluenesulfonic acid, etc., or a Lewis acid such as boron tribromide, aluminum chloride, etc., can be mentioned. As the base for this purpose, hydoxide of an alkali or alkaline earth metal such as sodium hydroxide, barium hydroxide, etc., an alkali metal carbonate such as sodium carbonate, calcium carbonate, etc., an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, etc., or sodium acetate, and the like can be used.

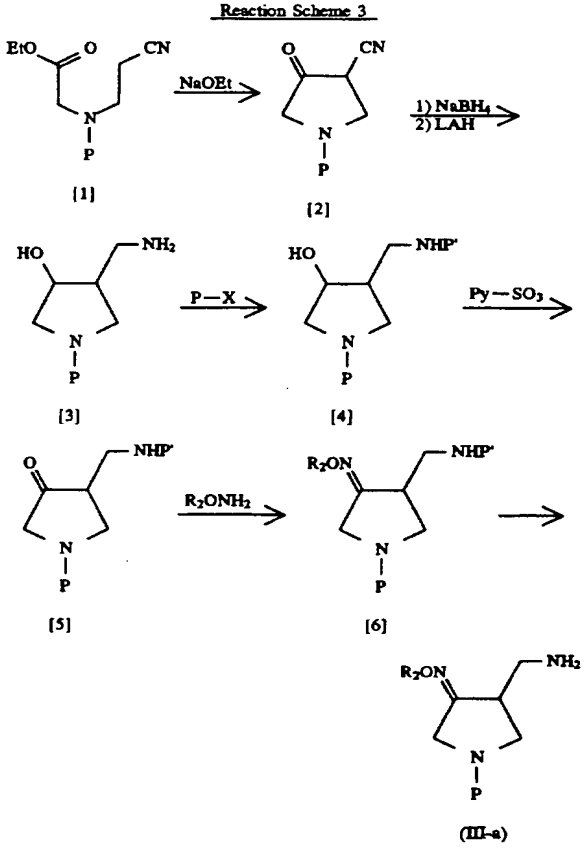
The reaction can be carried out in the presence of a solvent, for example, water or an organic solvent such as ethanol, tetrahydrofuran, dioxane, ethyleneglycol, acetic acid, etc., or a mixture of such organic solvent and water. If required, this reaction can also be practiced in the absence of any solvent.

In addition, when the protecting group is para-toluenesulfonyl, benzyl, trityl, para-methoxybenzyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, betaiodoethoxycarbonyl and the like, such groups can be effectively removed by means of a reduction. Although the reaction condition of the reduction for removing protecting group may be varied with properties of the relevant protecting group, the reduction can be generally carried out with hydrogen gas stream in an inert solvent in the presence of a catalyst such as platinum, palladium, Raney nickel, etc., at the temperature of 10° to 100° C. or with metal sodium or metal lithium in ammonia at the temperature of −50° to −10° C.

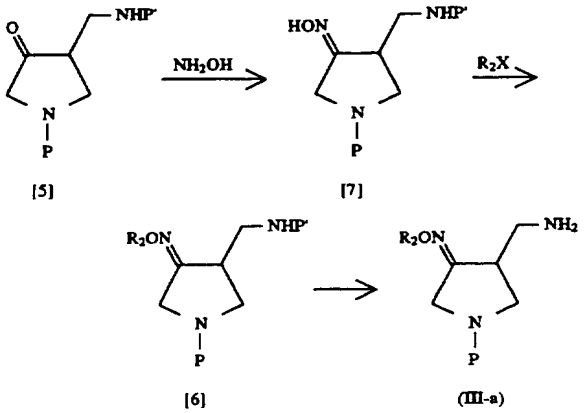
The compound of formula (II) used as the starting material in the present invention is a known compound and can be readily prepared according to a method known in the prior publication (see, J. M. Domagala, et al., J. Med. Chem. 34, 1142 (1991); J. M. Domagala, et al., J. Med. Chem. 31, 991 (1988); D. Bouzard, et al., J. Med. Chem. 35, 518 (1992)).

The compound of formula (III) used as another starting material in the present invention can be readily prepared according to the method as depicted in the following reaction schemes 3, 4 and 5.

Reaction Scheme 3



Reaction Scheme 4



In the above reaction schemes 3 and 4,

the protecting groups P and P' independently of one another represent the same amino-protecting group as defined for P in connection with the compound of formula (III') and can be identical wraith or different from each other; and

Py represents pyridine.

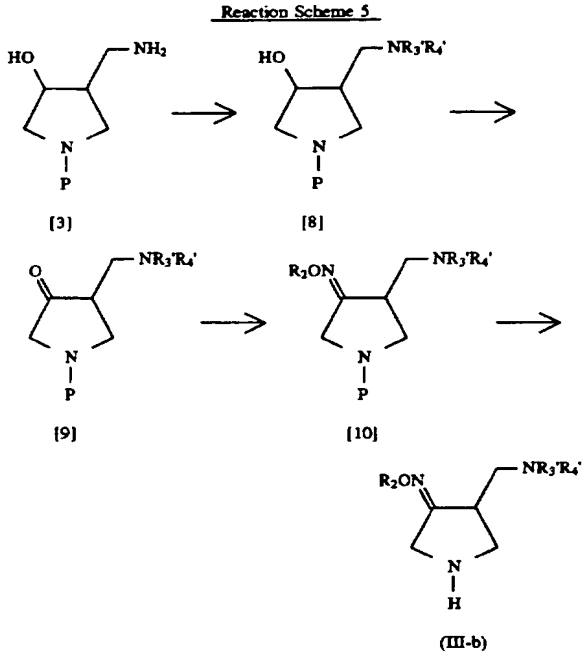
The process depicted in the reaction schemes 3 and 4 will be specifically explained hereinafter.

According to the reaction scheme 3, first a cyano ester [1] having a protected amino group can be reacted with sodium ethoxide in a solvent such as ethanol to obtain a 3-keto-4-cyanopyrrolidine [2]. The resulting cyanopyrrolidine [2] is reduced with hydrogen gas in the presence of a platinum catalyst to prepare an aminoalcohol [3]. In this case, the cyanopyrrolidine [2] may be reduced by means of other reductant to prepare the aminoalcohol [3]. For example, the ketone and cyano groups can be reduced with lithium aluminumhydride(LAH), sodium borohydride-cobalt chloride complex($NaBH_4$—$CoCl_3$) or lithium borohydride ($LiBH_4$). Alternatively, the aminoalcohol [3] can be synthesized by reducing first the ketone group to a hydroxyl group by means of sodium borohydride($NaBH_4$) and then reducing the cyano group by lithium aluminum hydride(LAH). Then, the amino group of the aminoalcohol [3] thus prepared is selectively protected to obtain a protected amine [4], which is then treated with sulfur trioxide(SO_3)-pyridine mixture in dimethylsulfoxide solvent (see, Parikh, J. R. and Doering, W. v. E. J. Am. Chem. Soc. 1967, 89, 5505), or oxidized with other oxidant, to prepare a ketone compound [5]. The resulting ketone compound [5] is then reacted with a O-substituted hydroxyamine of formula R_2ONH_2 to obtain the desired substituted oxime compound [6], which can be deprotected by means of a suitable method selected depending on the kind of protecting group to obtain the desired oxime compound (III) wherein R_3 and R_4 are hydrogen, i.e. the compound of formula (III-a).

Alternatively, according to the method depicted in the reaction scheme 4, the ketone compound [5] is reacted with hydroxyamine to obtain the desired oxime compound [7] and the compound [7] is reacted with a suitable electrophilic compound of formula R_2X which can introduce the desired R_2 group, in the presence of a base to prepare the oxime derivative of formula [6], which is then deprotected by means of a suitable method selected depending on the kind of protecting group in the same manner as in the reaction scheme 3 to prepare the desired oxime compound (III-a).

The compound of formula (III) wherein R_3 and R_4 of aminomethyl group present on 4-position of pyrrolidine are other than hydrogen, i.e. the compound of formula (III-b), can be prepared by the following reaction scheme 5.

Reaction Scheme 5



In the above reaction scheme,

$R_3{}^1$' and R_4' represent the same meaning as defined for R_3 and R_4 in connection with the compound of formula (I), provided that they cannot be hydrogen.

According to the method of reaction scheme 5, first the amine compound [3] is treated with C_1–C_3 aldehyde and then reduced to obtain a substituted amine compound [8] and the resulting amine compound [8] is treated with sulfur trioxide(SO_3)-pyridine mixture in dimethylsulfoxide solvent, or oxidized with other oxidant, to obtain a ketone compound [9]. The resulting ketone compound [9] can be treated in the same manner as in the method for treating ketone compound [5] in the reaction schemes 3 and 4 to synthesize the desired compound of formula (III-b).

The 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl) -1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate can be prepared by adding the methanesulfonic acid to the corresponding quinolone carboxylic acid compound in an amount of 0.95 to 1.5 times molar amount with respect to the quinolone carboxylic acid compound, or by adding the same amount of the methanesulfonic acid which is already dissolved in a solvent to the quinolone carboxylic acid compound. Although solvents suitable for the above preparation include C_1–C_4 haloalkanes, C_1–C_8 alcohols and water, a solvent selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroe- thane, methanol, ethanol, propanol, and water is preferred. If necessary, the quinolone carboxylic acid compound in a solvent may be heated to dissolve the former before the methanesulfonic acid is added. If the quinolone carboxylic acid compoundsolution exists as a suspension, acid may be added to the suspension to obtain a thoroughly transparent solution. The resulting reaction mixture is stirred for 1 to 24

hours at a temperature of −10° to 40° C. or is allowed to stand, then the product is obtained as a solid according as the solubility of the product decreases. The methanesulfonate can also be obtained in a high yield by removing the solvent used under reduced pressure.

The hydrates of the methanesulfonate of the present invention may easily be prepared by means of conventional methods well known in the art to which the present invention pertains. Particularly, the different hydrates may be prepared merely by changing recrystallization conditions.

The synthetic methods as described above will be more specifically explained in the following preparation examples.

The present invention also provides an antibacterial composition comprising the novel compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof as an active component together with a pharmaceutically acceptable carrier. When such antibacterial composition is used for clinical purpose, it may be formulated into solid, semi-solid or liquid pharmaceutical preparations for oral, parenteral or topical administration by combining the compound of formula (I) with a pharmaceutically acceptable inert carrier. The pharmaceutically acceptable inert carrier which can be used for this purpose may be solid or liquid. The solid or semi-solid pharmaceutical preparation in the form of powders, tablets, dispersible powders, capsules, cachets, suppositories and ointments may be prepared in which case solid carriers are usually used. The solid carrier which can be used is preferably one or more substances selected from the group consisting of diluents, flavouring agents, solubilizing agents, lubricants, suspending agents, binders, swelling agents, etc. or may be encapsulating substances. In the case of powder preparation, the micronized active component is contained in an amount of 5 or 10 to 70% in the carrier. Specific example of the suitable solid carrier includes magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectine, dextrin, starch, gelatin, tragaganth, methylcellulose, sodium carboxymethylcellulose, low boiling wax, cocoa butter, etc. Because of their ease in administration, tablets, powders, cachets and capsules represent the most advantageous solid preparation for oral administration.

The liquid preparation includes solutions, suspensions and emulsions. For example, the injectable preparation for parenteral administration may be in the form of water or waterpropyleneglycol solution, of which isotonicity, pH and the like can be adjusted to be suited for the physiological condition of living body. The liquid preparation can also be prepared in the form of a solution in aqueous polyethyleneglycol solution. The aqueous solution for oral administration can be prepared by dissolving the active component in water and adding a suitable coloring agent, flavouring agent, stabilizer and thickening agent thereto. The aqueous suspension suitable for oral administration can be prepared by dispersing the micronized active component in viscous substances such as natural or synthetic gum, methylcellulose, sodium carboxymethylcellulose and other known suspending agent.

It is especially advantageous to formulate the aforementioned pharmaceutical preparations in dosage unit form for ease of administration and uniformity of dosage. Dosage unit forms of the preparation refer to physically discrete units suitable as unitary dosage, each unit containing a predetermined quantity of the active component calculated to produce the desired therapeutic effect. Such dosage unit form can be in the packaged form, for example, a tablet, a capsule or a powder filled in vial or ampule, or an ointment, gel or cream filled in tube or bottle.

Although the amount of the active component contained in the dosage unit form can be varied, it can be generally adjusted within the range of 1 to 100 mg depending on the efficacy of the selected active component.

When the active compound of formula (I) of the present invention is used as a medicine for treatment of bacterial infections, it is preferably administered in an amount of about 6 to 14 mg per kg of body weight at the first stage. However, the administration dosage can be varied with the requirement of the subject patient, severity of the infections to be treated, the selected compound and the like.

The preferred dosage suitable for a certain condition can be determined by a person skilled in this art according to a conventional manner. In general, the therapeutic treatment is started from the amount less than the optimal dosage of the active compound and then the administration dosage is increased little by little until the optimal therapeutic effect is obtained. As a matter of convenience, the total daily dosage can be divided into several portions and administered over several times.

As mentioned above, the compound of the present invention shows a potent and broad spectrum antibacterial activity against various pathogenic organisms including gram-positive and gram-negative strains. The antibacterial activity of the present compound against gram-negative strains is comparable to or higher than that of the known antibacterial agents (for example, ciprofloxacin), and particularly, the antibacterial activity of the present compound against gram-positive strains is far superior to that of the known antibacterial agents. In addition, the present compound also exhibits a very potent antibacterial activity against the strains resistant to the known quinolone compounds.

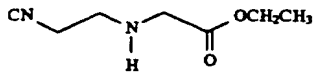
In view of the pharmacokinetic properties, the compound of the present invention has a high water-solubility and thus can be well absorbed in the living body, in comparison with the known quinolone compounds, to show a very high bioavailability. The biological half life of the present compound is far longer than that of the known quinolone compounds, and therefore, the present compound can be administered once a day to be suitably used as an antibacterial agent.

Moreover, since the compound according to the present invention is less toxic, it can be effectively used for prophylaxis and treatment of diseases caused by bacterial infections in warmblooded animals including human being.

The present invention will be more specifically explained in the following examples. However, it should be understood that the following preparations and examples are intended to illustrate the present invention and not to limit the scope of the present invention in any manner.

PREPARATION 1

Synthesis of (2-cyano-ethylamino)acetic acid ethyl ester



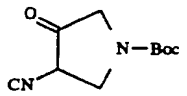
139.6 g (1 mole) of glycine ethyl ester hydrochloride was dissolved in 80 ml of distilled water and to this solution was added 230 ml of an aqueous solution of 67.3 g (1.2 mole eq.) of potassium hydroxide. Then, 106.2 g (2 mole eq.) of acrylonitrile was added to the reaction solution while heating and stirring at 50° to 60° C. The reaction mixture was stirred for 5 hours with heating and then the organic layer was separated. The aqueous layer was extracted with ethyl ether and the extract was combined with the organic layer as

separated above. The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to remove the solvent. The residue was distilled under reduced pressure (100° to 150° C./10.25torr) to obtain 65.6 g (Yield: 48%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 4.20(2H, q), 3.48(2H, s), 2.96(2H, t), 2.54(2H, t), 1.30(3H, t); MS (FAB, m/e): 157(M+H)

PREPARATION 2

Synthesis of 4-cyano-1-(N-t-butoxycarbonyl)-pyrrolidin-3-one

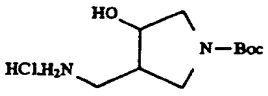


In the above formula and the following, Boc represents t-butoxycarbonyl. 29 g (0.186 mole) of the compound prepared in Preparation 1 was dissolved in 200 ml of chloroform and the resulting solution was introduced into a 1 L flask. Then, 45 g (1.1 mole eq.) of di-t-butoxycarbonyldicarbonate was added thereto and the reaction mixture was stirred for 17 hours at room temperature. The reaction solution was concentrated and the residue was diluted with 250 ml of absolute ethanol. The resulting solution was added to sodium ethoxide (NaOEt) solution prepared by adding 6 g of metal sodium (Na) turnings to 220 ml of absolute ethanol, under refluxing and heating. The reaction was continuously conducted for further one hour under refluxing with heating. The reaction solution was concentrated under reduced pressure and the residue was diluted with water and then washed with methylene chloride. The aqueous layer was adjusted with 1N HCl to pH 4 and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain a stoichiometric amount of the title compound in a crude state.

^{1}H NMR ($CDCl_3$, ppm):δ 6 4.5–3.5(5H, m), 1.5(9H, s); MS (FAB, m/e): 211(M+H)

PREPARATION 3

Synthesis of 4-aminomethyl-1-(N-t-butoxycarbonyl) pyrrolidin-3-ol hydrochloride

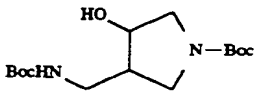


3 g (14 mmole) of the compound prepared in Preparation 2 was dissolved in the mixture of 357 ml of absolute ethanol and 7 ml of chlorofoirm and the resulting solution was introduced into a flask. Then, a catalytic amount of platinum oxide(PtO_2) was added thereto. After air was removed from the reaction flask under reduced pressure, the reaction mixture was stirred for 17 hours at room temperature with blowing up the hydrogen gas from a balloon filled with hydrogen gas. The reaction solution was filtered and the filtrate was concentrated to obtain a stoichiometric amount of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 8.0(2H, bs), 3.5–2.0(7H, m), 3.3(2H, s), 1.38(9H, s); MS (FAB, m/e): 217(M+H)

PREPARATION 4

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-ol



20 g (0.094 mole) of the compound prepared in Preparation 3 was dissolved in the mixture of 456 ml of dioxane and 263 ml of distilled water and the resulting solution was adjusted with 1N aqueous sodium hydroxide solution to pH 9. Then, 30.9 g (1.5 mole eq.) of di-t-butoxycarbonyldicarbonate was added thereto, and the reaction mixture was stirred for 30 minutes at room temperature and concentrated under reduced pressure. The residue was diluted with methylene chloride. After adding water to the reaction solution, the organic layer was separated and the aqueous layer was acidified to pH 4 and then extracted with methylene chloride. The extract was combined with the organic layer as separated above and the combined solution was dried over anhydrous magnesium sulfate and concentrated. The residue was purified with column chromatography to obtain 17 g (Yield: 57%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 4.95(1H, m), 4.1(1H, m), 3.5(2H, m), 3.3–3.0(4H, m), 2.1(1H, m), 1.45(18H, s); MS (FAB, m/e): 317(M+H)

Method B:

10 g (0.047 mole) of the compound prepared in Preparation 2 was introduced into a 1 L flask and then dissolved by adding 500 ml of dry tetrahydrofuran. This solution was cooled to −3° C. under ice-sodium chloride bath and then 3.8 g (0.094 mole) of lithium aluminumhydride(LAH) was added portionwise thereto over 20 minutes. After the addition is completed, the reaction mixture was stirred for one hour under ice-water bath. When the reaction is completed, 4 ml of water, 4 ml of 15% aqueous sodium hydroxide solution and 12 ml of water were carefully and successively added to the reaction mixture. The whole mixture was vigorously stirred for 3 hours at room temperature and 10 g of anhydrous magnesium sulfate was added thereto. This mixture was stirred and then filtered, and the filtrate was concentrated to stoichiometrically obtain the product. The resulting product was diluted with 200 ml of diozane-water (2:1 by volume) and 12.3 g (0.056 mole) of di-t-butoxycarbonyldicarbonate was added thereto at room temperature. The reaction solution was stirred for one hour at room temperature to complete-the reaction and then concentrated. The residue was diluted again with ethyl acetate, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and the residue was then purified with column chromatography using hexane-ethyl acetate (2:1 by volume) eluant to obtain 8.2 g (Yield: 55%) of the title compound.

Method C:

210 g (1 mole) of the compound prepared in Preparation 2 was dissolved in 4 L of methanol and this solution was introduced into a 6 L reaction vessel equipped with a thermometer. The internal temperature of the reaction vessel was cooled to 10° C. under dry ice-acetone bath. 76 g (2 mole) of sodium borohydride ($NaBH_4$) was added portionwise thereto over 1.5 hours while maintaining the internal temperature of the vessel at 10° to 13° C. After the addition is completed, the reaction mixture was stirred for further 30 minutes at the same temperature so that all the ketone can be reduced to alcohol. Then, 243 g (1 mole) of cobalt chloride hydrate was added thereto over 10 minutes. When the reaction is completed, the resulting solid complex was

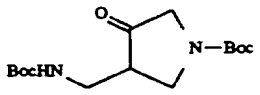
dissolved in 4 L of ammonia water and this solution was diluted with 8 L of water and then extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and mixed with the mixture of 1.5 L of dioxane and 0.5 L of distilled water. 212 g of di-t-butoaycarbonyldicarbonate was added thereto and the whole mixture was stirred for 2 hours at room temperature. After the react ion is completed, the reaction mixture was concentrated under reduced pressure, diluted again with dichloromethane, washed with water, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and then purified with silica gel column chromatography (eluant: hexaneethyl acetate 2:1 by volume) to obtain 202 g (Yield: 64%) of the title compound.

Method D:

10 g (0.047 mole) of the compound prepared in Preparation 2 was introduced into a 1 L flask and dissolved by adding 500 ml of methanol. This solution was cooled down under ice bath and 3.6 g (0.094 mole) of sodium borohydride was added portionwise thereto over 20 minutes. The reaction mixture was stirred for further 30 minutes to complete the reaction, and then concentrated under reduced pressure, diluted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain the compound in which the desired ketone group is reduced to an alcohol. 10.1 g (0.047 mole) of the resulting alcohol compound was dissolved in 200 ml of dry tetrahydrofuran and this solution was cooled down to −5° C. under ice-salt bath. 2.6 g (0.066 mole) of lithium aluminumhydride was added thereto over 20 minutes. The reaction mixture was stirred for further 30 minutes at the same temperature to complete the reaction, and then 2.6 ml of water, 2.6 ml of 15% sodium hydroxide and 7.8 ml of water were added in order thereto. This mixture was stirred for one hour at room temperature. After adding 6 g of anhydrous magnesium sulfate, the mixture was stirred for further 30 minutes and filtered. The filtrate was concentrated to obtain the product. The resulting product was diluted with 200 of dioxane-water (2:1 by volume) and 12.3 g (0.056 mole) of di-t-butoxycarbonyldicarbonate was added portionwise thereto. The mixture was stirred for 30 minutes to complete the reaction, and then concentrated, diluted with ethyl acetate, washed with saturated saline, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was purified with column chromatography to obtain 12.3 g (Yield: 83%) of the title compound.

PREPARATION 5

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-one

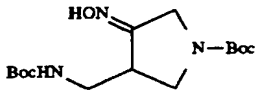


14 g (0.044 mole) of the compound prepared in Preparation 4 was dissolved in 64 ml of dimethylsulfoxide and 18.5 ml (3 mole eq.) of triethylamine was added thereto. This mixture was cooled down under ice bath. When the wall of reaction flask begins to freeze, 12.7 g (1.8 mole eq.) of pyridine-sulfur trioxide(Py-SO_3) oxidant was added portionwise thereto. After the addition is completed, the ice bath was removed and the reaction solution was stirred for 3 hours at room temperature, diluted with water and then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated to stoichiometrically obtain the title compound in a crude state.

^{1}H NMR ($CDCl_3$, ppm): δ 4.95(1H, bs), 4.15–2.7(6H, m), 2.8 (1H, br), 1.45(9H, s), 1.40(9H, s); MS (FAB, m/e): 315 (M+H)

PREPARATION 6

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)amino-methyl-pyrrolidin-3-one oxine

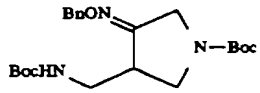


300 mg of the compound prepared in Preparation 5 was dissolved in the mixture of 6 ml of 95% ethanol and 3 ml of tetrahydrofuran(THF) and this solution was introduced into a 30 ml reaction vessel. 232 mg (3.5 mole eq.) of hydroxyamine hydrochloride (NH_2OH·HCl) was added thereto and then 281 mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5 ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40° C. under oil bath to complete the reaction, cooled down and then concentrated under reduced pressure. The residue was diluted with ethylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 230 mg (Yield: 73%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 9.70(1H, bs), 5.05(1, bs), 4.2(2H, br), 3.83(1H, m), 3.5–3.2(3H,m), 3.0(1H, m), 1.42 (18H, s); MS (FAB, m/e): 330(M+H)

PREPARATION 7

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)amino-methyl-pyrrolidin-3-one-benzyloxime

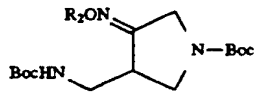


659 mg of the compound prepared in Preparation 6, 193 mg of tetra-n-butylammonium bromide and 855 mg of benzyl bromide were added to 15 ml of dichloromethane and then 5 ml of 15% aqueous sodium hydroxide solution was added thereto. The reaction mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776 mg (Yield: 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 7.33(5H, m), 5.13(2H, s), 4.92(1H, m), 4.13(2H, m), 3.76(1H, m), 3.41(1H, m), 3.25 (2H m), 3.02(1H, m), 1.50(9H, s), 1.49(9H, s); MS (FAB, m/e): 420(M+H)

PREPARATIONS 8 TO 17

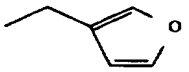
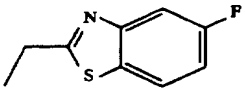
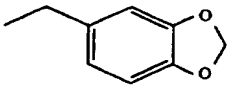
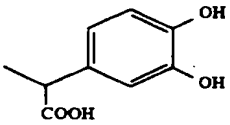
The amine compounds listed in the following Table 1 were prepared according to the same procedure as Preparation 7 except that the corresponding benzylbromide derivatives having R_2 structure as presented in the following Table 1 are used instead of benzylbromide.



^{1}H NMR (DMSO-d_6, ppm): δ 10.0(1H, m), 8.35(2H, m), 7.40(5H, m), 5.18(2H, s), 4.00(2H, m), 3.69(1H, m), 3.40 (2H, m), 3.12(2H, s); MS (FAB, m/e): 220(M+H)

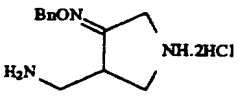
TABLE 1

Preparations 8 to 17

Prep.	R_2	NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
8	4-nitrobenzyl	8.2(2H, m), 7.4(2H, m), 5.2(2H, s), 4.9(1H, s), 4.2(2H, m), 3.8(1H, m), 3.5–3.2(3H, m), 3.0(1H, m), 1.5(18H, s)	465
9	4-methoxybenzyl	7.3(2H, m), 6.9(2H, m), 5.0(2H, s), 4.9(1H, s), 4.1(2H, m), 3.8(3H, s), 3.75(1H, m), 3.5–3.0(4H, m), 1.45(18H, s)	450
10	4-fluorobenzyl	7.3(2H, m), 7.0(2H, m), 5.0(2H, s), 4.8(1H, br), 4.2(2H, m), 3.9(1H, m), 3.4(3H, m), 3.0(1H, m), 1.46(18H, s)	438
11	4-t-butylbenzyl	7.4–7.3(4H, m), 5.1(2H, s), 5.0(1H, s), 4.1(2H, m), 3.8(1H, m), 3.6–3.0(4H, m), 1.45(18H, s), 1.3(9H, s)	476
12	2-cyanobenzyl	7.8–7.3(4H, m), 5.3(2H, s), 5.0(1H, bs), 4.2(2H, s), 3.9(1H, m), 3.6–3.2(3H, m), 3.0(1H, s), 1.5(18H, s)	445
13	3-pyridylmethyl	8.6(2H, m), 7.7(1H, m), 7.3(1H, m), 5.1(2H, s), 4.9(1H, s), 4.1(2H, m), 3.8(1H, m), 3.6–3.2(3H, m), 3.0(1H, m), 1.5(18H, s)	421
14		7.4(2H, m), 6.5(1H, m), 4.9(2H, s), 4.9(1H, s), 4.1(2H, m), 3.8(2H, m), 3.2(3H, m), 1.5(18H, s)	410
15		7.7(2H, m), 7.2(1H, m), 5.5(1H, s), 5.0(1H, s), 4.2(2H, m), 3.8(1H, m), 3.6–3.1(4H, m), 1.5(18H, s)	495
16		6.9(3H, m), 6.0(2H, m), 5.0(3H, m), 4.1(2H, m), 3.8(1H, m), 3.6–3.2(3H, m), 3.0(1H, m), 1.5(18H, s)	464
17		7.3–7.0(3H, m), 6.8(1H, s), 5.1(1H, s), 4.2(2H, m), 3.8(1H, m), 3.5–3.0(4H, m), 1.6–1.4(27H, s)	496

PREPARATION 18

Synthesis of 4-aminomethyl-pyrrolidin-3-one-benzyloxime dihydro-chloride



20 ml of methanol was cooled down to 5° C. and then 10 ml of acetyl chloride was slowly added thereto. This mixture was stirred for 30 minutes and 990 mg of the compound prepared in Preparation 7, which is dissolved in 10 ml of methanol, was added thereto. The reaction mixture was stirred for 50 minutes at room temperature and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to obtain 648 mg (Yield: 94%) of the title compound as a yellow solid.

PREPARATIONS 19 TO 23

The compounds listed in the following Table 2 were prepared from the amine compounds prepared in Preparations 8 to 17 according to the same procedure as Preparation 18.

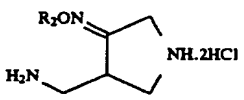
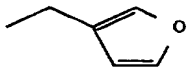
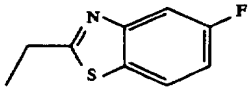
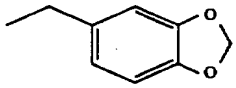
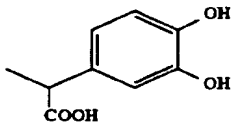


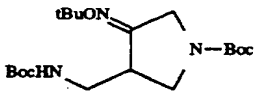
TABLE 2

Preparations 19 to 28

Prep.	R_2	NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
19	4-nitrobenzyl	10.3–10.1(2H, s), 8.3(3H, s), 8.2(2H, d), 7.7(2H, d), 5.3(2H, s), 4.1(2H, m), 3.7(1H, m), 3.4(2H, m), 3.1(2H, m)	265
20	4-methoxybenzyl	10.2–10.0(2H, s), 8.4(3H, s), 7.3(2H, d), 6.9(2H, d), 5.0(2H, s), 3.9(2H, m), 3.73(3H, s), 3.7(1H, m), 3.4(2H, m), 3.1(2H, m)	250
21	4-fluorobenzyl	10.2(2H, s), 8.4(3H, s), 7.3(2H, m), 7.2(2H, m), 5.1(2H, s), 3.9(2H, m), 3.7(1H, m), 3.4(2H, m), 3.1(2H, m)	238
22	4-t-butylbenzyl	10.2(2H, s), 8.4(3H, s), 7.4–7.3(4H, m), 5.1(2H, s), 3.9(2H, m), 3.7(1H, m), 3.2 (2H, m), 3.1(2H, m), 1.3(9H, s)	276
23	2-cyanobenzyl	10.2–10.0(2H, s), 8.2(3H, s), 7.9–7.5(4H, m, 5.3(2H, s), 4.0(2H, m), 3.7(1H, m), 3.2(2H, m), 3.1(2H, m)	245
24	3-pyridylmethyl	10.3(1H, s), 10.1(1H, s), 8.9(1H, s), 8.8 (1H, m), 8.5(1H, d), 8.4(3H, m), 8.0(1H, m), 5.4(2H, s), 4.0(2H, m), 3.7(1H, m), 3.4 (2H, m), 3.1(2H, m)	221
25		10.3(2H, s), 8.4(3H, s), 7.6(1H, s), 6.4(1H, s), 5.0(2H, s), 4.0(2H, m), 3.8(1H, m), 3.4(2H, m), 3.1(2H, m)	210
26		10.3(2H, s), 8.3(3H, s), 8.1(1H, m), 7.9 (1H, m), 7.4(1H, m), 5.5(2H, s), 4.1(2H, m), 3.9(1H, m), 3.14(2H, m), 3.1(2H, m)	295
27		10.2(2H, s), 8.3(3H, s), 7.0(3H, m), 6.3 (2H, s), 5.3(2H, m), 4.1(2H, m), 3.9(1H, m), 3.4–3.2(2H, m), 3.1(2H, m)	264
28		10.3–10.2(2H, s), 8.4(3H, s), 8.0–7.3(3H, m), 7.0(1H, s), 4.2(2H, m), 3.8(1H, m), 3.5–3.2(3H, m), 3.0(1H, m)	296

PREPARATION 29

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)amino-methyl-pyrrolidin-3-one t-butyloxime

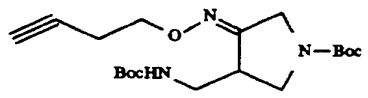


300 mg of the compound prepared in Preparation 5 was dissolved in the mixture of 6 ml of 95% ethanol and 3 ml of tetrahydrofuran(THF) and this solution was introduced into a 30 ml reaction vessel. 487 mg (3.5 mole eq.) of o-t-butylhydroxyamine hydrochloride was added thereto and then 281 mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5 ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40° C. under oil bath to complete the reaction, and then cooled down, concentrated under reduced pressure, diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume to obtain 285 mg (Yield: 80%) of the title compound.

^1H NMR ($CDCl_3$, ppm): δ 5.10(1H, bs), 4.05(2H, s), 3.71(1H, dd), 3.43(1H, br), 3.2(2H, m), 3.0(1H, m), 1.42 (13H, s), 1.30(9H, s); MS (FAB, m/e): 386(M+H)

PREPARATION 30

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)amino-methyl-pyrrolidin-3-one 3-butynyloxime



A. Synthesis of 3-butynyl hydroxylamine

0.35 g (5 mmole) of 3-butynol, 0.86 g (5.25 mmole) of N-hydroxyphthalimide and 1.44 g (5.5 mmole) of triphenylphosphine were dissolved in 15 ml of dry tetrahydrofuran, and then 1.05 g (6 mmole) of diethylazodicarboxylate was added thereto over 30 minutes. The mixture was stirred for 10 minutes at room temperature and then distilled under reduced pressure to remove the solvent. To the residue was added 50 ml of ethyl acetate-hexane (1:1 v/v). The precipitated solid material was filtered off and the filtrate was concentrated. The residue was purified with column chromatography (hexane-ethyl acetate 9:1 v/v). The

resulting white solid [0.54 g. Yield 50%. ^{1}H NMR ($CDCl_3$, ppm): δ 7.35(2H. m). 7.75(2H. m). 4.2(2H. t). 2.8(2H. dd). 2.5(2H. dd). 2.1(1H. s). FAB MS(POS): $[M+H]^+$=216] was dissolved in 12 ml of methylene chloride. and 0.25 g (5 mmole) of hydrazine hydrate diluted with 4 ml of methanol was added dropwise thereto. The solid precipitate was filtered off and the filtrate was concentrated at low temperature under reduced pressure to obtain 0.2 g (Yield: 93%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 9.5(2H. br). 4.5(2H. t). 2.8(2H. m). 2.4(2H. m). 2.05(1H. s); MS (FAB. m/e): $86(M+H)^+$

B. Synthesis of the Title Compound

0.45 g (1.43 mmole) of the compound prepared in Preparation 5 and 0.2 g (2.35 mmole) of 3-butynyl hydroxyamine were dissolved in 5 ml of methanol and the reaction was conducted for 12 hours at 60° C. The reaction solution was concentrated under reduced pressure and the residue was subjected to column chromatography (ethyl acetate-hexane 1:4 v/v) to obtain 0.59 g (stoichiometric amount) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 5.0(1H. m). 4.15(2H. t). 4.0(2H. s). 3.75(1H. m). 3.6–3.2(3H. m). 3.0(1H. m). 2.5 (2H. m). 2.0(1H. s). 1.45(18H. s); FAB MS (POS): $332(M+H)^+$

PREPARATIONS 31 TO 36

The amine compounds listed in the following Table 3 were prepared according to the procedure as Preparation 30 except that the corresponding alcohol derivatives having R_2 structure as represented in the following Table 3 are used instead of 3-butynol.

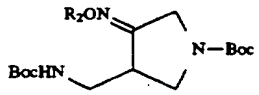
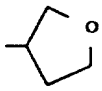


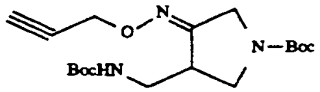
TABLE 3

Preparations 31 to 36

Prep.	R_2	^{1}H NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
31	isopropyl	5.0(1H, br), 4.1(2H, s), 4.0(1H, m), 3.4 (1H, m), 3.55–3.25(3H, m), 3.0(1H, m), 1.55(18H, s), 1.0(6H, d)	372
32	cyclobutyl	4.7(1H, m), 4.2(2H, s), 3.8(1H, m), 3.4(1H, m), 3.3(2H, m), 3.0(1H, m), 2.3(2H, m), 2.1 (2H, m), 1.8(1H, m), 1.6(1H, m), 1.5(18H, s)	384
33	cyclopentyl	4.7(1H, m), 4.1(2H, m), 3.7(1H, m), 3.4(1H, m), 3.3(2H, m), 3.0(1H, m), 1.8(4H, m), 1.7(4H, m), 1.6(18H, s)	398
34		5.0–4.8(1H, m), 4.3–3.7(6H, m), 3.3(2H, m), 3.0(1H, m), 2.1(2H, m), 1.5(18H, s), 1.3(2H, m)	400
35	cyclopropyl-methyl	5.1(1H, br), 4.1(2H, m), 3.9(2H, m), 3.8(1H, m), 3.5(1H, m), 3.3(2H, m), 3.0(1H, m), 1.5 (18H, s), 1.1(1H, m), 0.6(2H, s), 0.3(2H, s)	384
36	isobutyl	5.05(1H, br), 4.15(2H, s), 4.1(2H, d), 3.6(2H, m), 3.3(1H, m), 3.0(2H, m), 2.5(1H, m), 1.5(18H, s), 1.05(6H, d)	386

PREPARATION 37

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)amino-methyl-pyrrolidin-3-one propargyl oxime



659 mg of the compound prepared in Preparation 6. 193 mg of tetra-n-butylammonium bromide and 855 mg of propargyl bromide were added to 15 ml of dichloromethane. and 5 ml of 15% aqueous sodium hydroxide solution was added thereto. This mixture was stirred for 30 minutes at room temperature. The organic layer was separated. dried over anhydrous magnesium sulfate and then filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776 mg (Yield: 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): δ 6 4.92(1H. m). 4.13(2H. m). 3.76(1H. m). 3.41(1H. m). 3.25(2H. m). 3.02(1H. m). 1.50 (9H. s). 1.49(9H. s); MS (FAB. m/e): 368(M+H)

PREPARATIONS 38 AND 39

The amine compounds listed in the following Table 4 were prepared according to the same procedure as Preparation 37 except that the corresponding alkyl derivatives having R_2 structure as represented in the following Table 4 are used instead of propargyl.

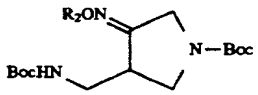


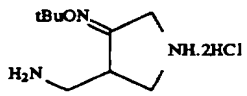
TABLE 4

Preparations 38 and 39

Prep.	R_2	^1H NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
38	methoxymethyl	5.15–4.9(3H), 4.15(2H, m), 3.75 (1H, m), 3.5–3.2(5H), 3.0(1H, m), 1.5(18H, s)	374
39	2-chloroethyl	4.9(1H, m), 4.30(2H, t), 4.1(2H, s), 3.7(3H, m), 3.6(1H, m), 3.5–3.0(3H, m), 1.45(18H, s)	392

PREPARATION 40

Synthesis of 4-aminomethyl-pyrrolidin-3-one t-butyloximne dihydro-chloride



5 ml of methanol was cooled down to 0° C. and 3 ml of acetyl chloride was slowly added thereto. This mixture was stirred for 10 minutes and 640 mg of the compound prepared in Preparation 29, which is dissolved in 10 ml of methanol, was added thereto. The reaction mixture was stirred for 20 minutes at room temperature and concentrated under reduced pressure. The residue was filtered, washed with ethylether and dried to obtain 390 mg (Yield: 91%) of the title compound as a white solid.

^1H NMR (DMSO-d_6, ppm): δ 10.0–9.6(2H, bsX2), 8.20 (3H, br), 3.90(2H,dd), 3.61(1H, bs), 3.40(2H, bs), 3.12(2H, bs), 1.25(9H, s); MS (FAB, m/e): 186(M+H)

PREPARATIONS 41 TO 50

The compounds of Preparations 41 to 50 as listed in the following Table 5 were prepared from the compounds prepared in Preparations 30 to 40 according to the same procedure as Preparation 40.

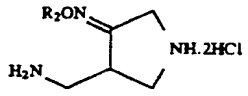
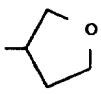


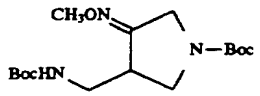
TABLE 5

Preparations 41 to 50

Prep.	R_2	^1H NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
41	$CH_2CH_2C\equiv CH$	10.1–9.8(2H, br), 8.2(3H, br), 4.3(2H, t), 4.0(2H, s), 3.7(1H, m), 3.6–3.2(3H, m), 3.0(1H, m), 2.8(1H, s), 2.6(2H, t)	182
42	isopropyl	10.1–9.8(2H, br), 8.3(3H, br), 4.4(1H, m), 3.9(2H, d), 3.7(1H, m), 3.3(2H, s), 3.1(2H, m), 1.2(6H, d)	172
43	cyclobutyl	10.2–9.8(2H, br), 8.2(3H, br), 4.8(1H, m), 4.3(2H, s), 3.7(1H, m), 3.6–3.2(3H, m), 3.0(1H, m), 1.8(2H, m), 1.7(2H, m), 1.5(1H, m), 1.45(1H, m)	184
44	cyclopentyl	10.2–9.8(2H, br), 8.2(3H, br), 4.7(1H, m), 4.3(2H, s), 3.8(1H, m), 3.3(1H, m), 3.2(3H, m), 1.8(4H, m), 1.6(2H, m), 1.5(2H, m)	198
45		10.1–9.8(2H, br), 8.3(3H, s), 4.1–3.6 (10H, m), 3.2(2H, s), 2.2–1.9(2H, m)	200
46	cyclopropyl-methyl	10.1–9.8(2H, br), 8.3(3H, s), 4.0–3.8 (4H, m), 3.65(1H, m), 3.4(2H, m), 3.1(2H, m), 1.1(1H, m), 0.5(2H, d), 0.2(2H, d)	184
47	isobutyl	10.3–9.9(2H, br), 8.4(3H, br), 3.9–3.8 (4H, m), 3.65(1H, m), 3.3(2H, s), 3.1(2H, m), 1.9(1H, m), 0.85(6H, d)	186
48	propargyl	10.0(1H, m), 8.3(2H, m), 4.8(2H, s), 4.0(2H, m), 3.7(1H, m), 3.6(1H, s) 3.4(2H, m), 3.1(2H, s)	168
49	methoxymethyl	10–9.6(2H, br), 8.2(3H, br), 5.1(2H, dd) 4.1–3.8(2H, m), 3.7(1H, m), 3.3–3.0(4H, m)	174
50	2-chloroethyl	10–9.7(2H, br), 8.2(3H, br), 4.3(2H, t), 4.0(2H, m), 3.8(2H, t), 3.7(1H, m), 3.4(2H, m), 3.2(1H, m), 3.1(2H, m)	192

PREPARATION 51

Synthesis of 4-(N-t-butoxycarbonylaminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-one O-methyloxime



260 mg (8.23×10^{-4} mole) of the compound prepared in Preparation 5 was dissolved in the mixture of 5 ml of 95% ethanol and 2.5 ml of tetrahydrofuran and this solution was introduced into a reaction vessel. Then, 256 mg (3.7 mole eq.) of methoxyamine hydrochloride was added thereto and 257 mg (3.7 mole eq.) of sodium hydrogen carbonate ($NaHCO_3$) dissolved in 2.5 ml of distilled water was also added. The reaction mixture was stirred for 1 hours at 40° C. under oil bath, concentrated under reduced pressure, washed successively with aqueous ammonium chloride solution and aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain 250 g (Yield: 88%) of the title compound.

^{1}H NMR($CDCl_3$, ppm): δ 4.98(1H, bs), 3.81(3H, s), 3.75–2.80(7H, m), 1.40(1H, s); MS (FAB, m/e): 344(M+H)

PREPARATIONS 52 AND 53

The compounds listed in the following Table 6 were prepared according to the same procedure as Preparation 51 except that phenoxyamine hydrochloride or ethoxyamine hydrochloride are used instead of methoxyamine hydrochloride.

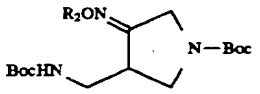


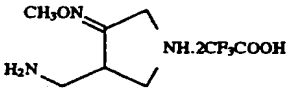
TABLE 6

Preparations 52 and 53

Prep.	R_2	^{1}H NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
52	phenyl	7.3(5H, m), 4.97(1H, bs), 3.8–2.8 (7H, m), 1.40(18H, s)	406
53	$-CH_2CH_3$	5.0(1H, bs), 3.8–2.8(7H, m), 1.42 (18H, s), 1.41(18H, s), 1.38(3H, t)	358

PREPARATION 54

Synthesis of 4-aminomethyl-pyrrolidin-3-one O-methyloxime ditrifluoroacetate



5 ml of trifluoroacetic acid was added to 250 mg of the compound prepared in Preparation 51, and this mixture was stirred for 20 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, dissolved in the smallest amount of acetonitrile and then solidified with ethylether to obtain 220 mg (Yield: 84%) of the title compound in a purified state.

^{1}H NMR (CD_3OD, ppm): δ 4.1(2H, s), 3.96(3H, s), 3.83(1H, dd), 3.7–3.2(6H, m); MS (FAB, m/e): 144(M+H)

PREPARATIONS 55 TO 57

The corresponding compounds of Preparations 55 to 57 were prepared from the compounds prepared in Preparations 6, 52 and 53, respectively, according to the same procedure as Preparation 54.

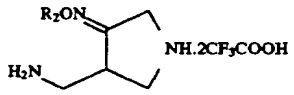


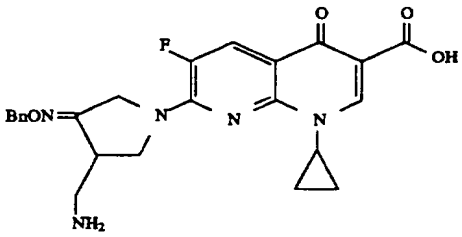
TABLE 7

Preparations 55 to 57

Prep.	R_2	^{1}H NMR ($CDCl_3$), δ (ppm)	FAB MS (M + H)
55	—H	4.1–3.2(7H, m)	130
56	-Ph	7.2–7.4(5H, m), 4.1–3.2(7H, m)	206
57	$-CH_2CH_3$	4.2–3.1(9H, m), 1.3(3H, t)	158

EXAMPLE 1

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



622 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 643 mg of the compound prepared in Preparation 18 were suspended in 15 ml of acetonitrile. This suspension was cooled down under ice-water bath and then 1.0 ml of 1,8-diazabicyclo [5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 1.5 hours at room temperature and, after adding 15 ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 504 mg (Yield: 57%) of the title compound.

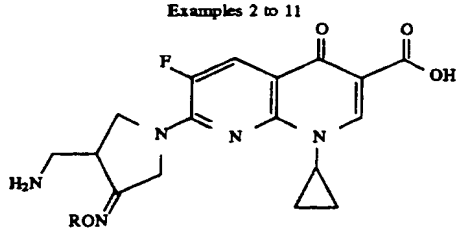
^{1}H NMR (DMSO-d_6, ppm): δ 8.59(1H, s), 8.03(1H, d), 7.40(5H, m), 5.14(2H, s), 4.75(2H, s), 4.18(1H, m), 3.94 (1H, m), 3.83(1H, m), 3.35(2H, m), 3.05(1H, m), 2.81(1H, m), 2.73(1H, m), 1.25–1.05(4H, m); MS (FAB, m/e): 466 (M+H)

EXAMPLES 2 TO 11

The same starting material as Example 1 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 1 to prepare the respective compounds listed in the following Table 8.

TABLE 8

Examples 2 to 11



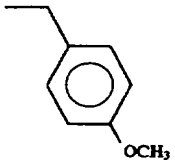
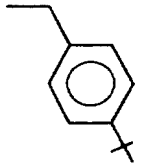
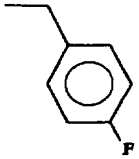
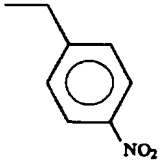
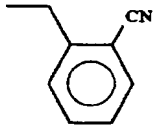
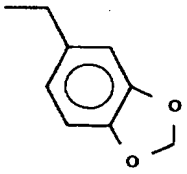
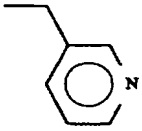
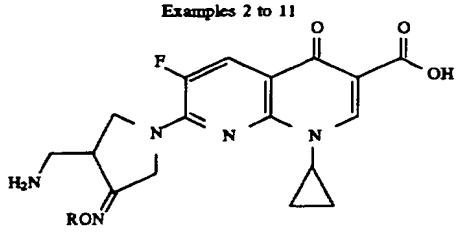
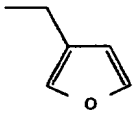
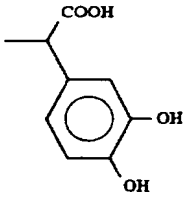
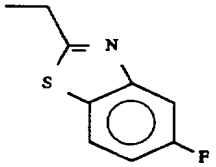
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
2		8.73(1H, s), 8.05(1H, d), 7.30 (2H, d), 6.98(2H, d), 5.10(2H, s), 4.61(2H, s), 4.25(1H, m), 3.90(1H, m), 3.80(3H, s), 3.70 (1H, m), 3.00(3H, m), 1.26(2H, m), 1.07(2H, m)	$CDCl_3$	496	10	75
3		8.75(1H, s), 8.05(1H, d), 7.45 (2H, d), 7.30(2H, d), 5.15(2H, s), 4.62(2H, s), 4.25(1H, m), 3.85(1H, m), 3.75(1H, m), 3.10 (1H, m), 2.98(2H, m), 1.35(9H, s), 1.25(2H, m), 1.09(2H, m)	$CDCl_3$	522	15	76
4		8.68(1H, s), 8.00(1H, d), 7.35 (2H, m), 7.10(2H, m), 5.08(2H, s), 4.59(2H, s), 4.20(1H, m), 3.95(1H, m), 3.81(1H, m), 3.00 (3H, m), 1.23(2H, m), 1.04(2H, m)	$CDCl_3$	484	15	80
5		8.59(1H, s), 8.21(2H, d), 8.06 (1H, s), 7.64(2H, d), 5.29(2H, s), 4.68(2H, s), 4.20(1H, m), 3.95(1H, m), 3.85(1H, m), 3.10 (1H, m), 2.80(2H, m), 1.18(2H, m), 1.10(2H, m)	DMSO	511	10	76
6		8.58(1H, s), 8.05(1H, d), 7.92–7.42(4H, m), 5.28(2H, s), 4.65(2H, s), 4.20(1H, m), 3.95 (1H, m), 3.78(1H, m), 3.10(1H, m), 2.80(2H, m), 1.20(2H, m), 1.09(2H, m)	DMSO	491	20	82
7		8.74(1H, s), 8.10(1H, d), 6.92 (3H, m), 6.10(2H, s), 5.10(2H, s), 4.75(2H, s), 4.30(1H, m), 3.95(1H, m), 3.85(1H, m), 3.15 (1H, m), 3.10(2H, m), 1.28(2H, m), 1.09(2H, m)	$CDCl_3$	510	25	79
8		8.60(1H, d), 8.57(1H, s), 8.52 (1H, d), 8.03(1H, d), 7.80(1H, d), 7.41(1H, q), 5.18(2H, s), 4.65(2H, s), 4.17(1H, m), 3.94 (1H, m), 3.75(1H, m), 3.30(2H, m), 3.04(1H, m), 2.81(1H, m), 2.73(1H, m), 1.30–1.00(4H, m)	DMSO-d_6	467	90	70

TABLE 8-continued

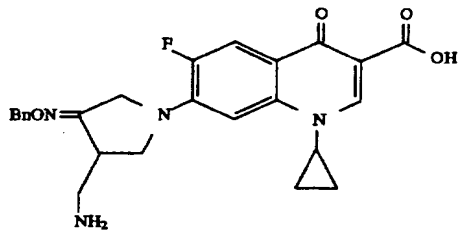
Examples 2 to 11



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
9		8.82(1H, s), 8.05(1H, d), 7.51 (1H, d), 7.45(1H, m), 6.5(1H, s), 5.02(2H, m), 4.5(2H, m), 4.20(1H, m), 3.95(1H, m), 3.70 (1H, m), 3.00(1H, m), 2.80(1H, m), 2.70(1H, m), 1.00(4H, m)	DMSO	456	15	69
10		8.58(1H, s), 8.00(1H, d), 7.10 (3H, m), 6.72(1H, s), 4.80(2H, s), 4.20(1H, m), 3.95(1H, m), 3.85(1H, m), 3.10(1H, m), 2.95 (2H, m), 1.07(4H, m)	DMSO	542	20	65
11		8.76(1H, s), 8.20(1H, m), 8.02 (1H, d), 7.89(1H, m), 7.40(1H, m), 5.60(2H, s), 4.78(2H, m), 4.45(1H, m), 3.85(1H, m), 3.70 (1H, m), 3.10(2H, m), 1.30(2H, m), 1.15(2H, m)	DMSO	541	25	73

EXAMPLE 12

Synthesis of 7-(4-animomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclcopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



530 mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile. This suspension was cooled down under ice-water bath and then 913 mg of 1,8-diazabicyclo[5.4.0] undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80° C. and, after adding 15 ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 631 mg (Yield: 68%) of the title compound.

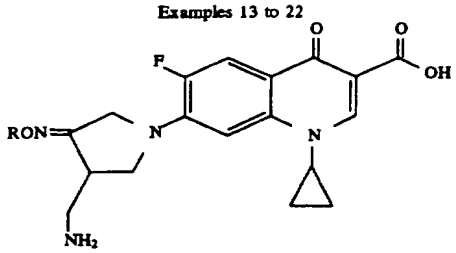
^{1}H NMR (DMSO-d_6, ppm): δ 8.60(1H, s), 7.92(1H, d), 7.38(5H, m), 5.10(2H, s), 4.87(2H, s), 4.10(1H, m), 3.94 (1H, m), 3.86(1H, m), 3.37(2H, m), 3.02(1H, m), 2.38(1H, m), 2.73(1H, m), 1.25–1.05(4H, m) MS (FAB, m/e): 465 (M+H)

EXAMPLES 13 TO 22

The same starting material as Example 12 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 12 to prepare the respective compounds listed in the following Table 9.

TABLE 9

Examples 13 to 22



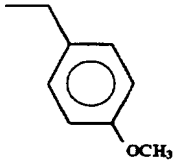
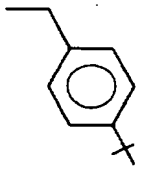
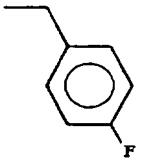
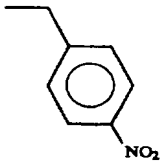
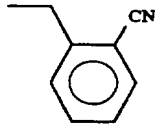
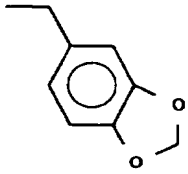
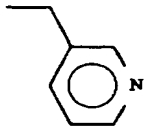
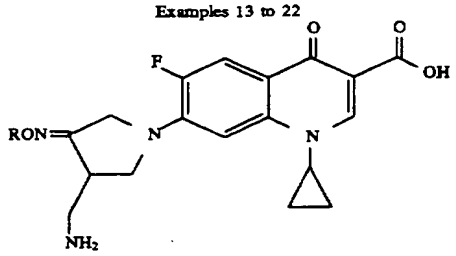
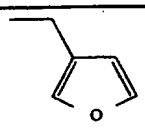
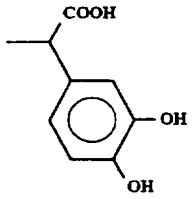
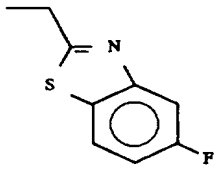
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB. MS (M + 1)	Reac. time (hr)	Yield (%)
13		8.6(1H, s), 7.8(1H, d), 7.2(3H, d), 6.9(2H, d), 5.1(2H, s), 4.4 (2H, s), 3.9(1H, m), 3.8(1H, m), 3.7(3H, s), 3.65(1H, m), 3.0 (1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	495	2	60
14		8.6(1H, s), 7.8(1H, d), 7.4(2H, d), 7.3(3H, m), 5.1(2H, s), 4.4 (2H, s), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.4(9H, s), 1.3–1.1 (4H, m)	DMSO-d_6	521	2	65
15		8.6(1H, s), 7.8(1H, d), 7.4(2H, m), 7.2(3H, m), 5.1(2H, s), 4.4 (2H, s), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.3–1.1(4H, m)	DMSO-d_6	483	4	67
16		8.6(1H, s), 8.2(2H, d), 7.8(1H, d), 7.6(2H, d). 7.2(1H, d), 5.3 (2H, s), 4.4(2H, s), 3.9(1H, m), 3.8(1H,m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1 (4H, m)	DMSO-d_6	510	3	58
17		8.6(1H, s), 7.9–7.4(5H, m), 7.2 (1H, d,), 5.3(2H, s), 4.4(2H, s), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	490	4	55
18		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 6.9(3H, m), 6.1(2H, s), 5.1 (2H, s), 4.4(2H, s), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1 (4H, m)	DMSO-d_6	509	4	71
19		8.6(3H, m), 7.8(2H, m), 7.4(1H, q), 7.2(1H, d), 5.2(2H, s), 4.4 (1H, m), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.3–1.1(4H, m)	DMSO-d_6	466	4	53

TABLE 9-continued

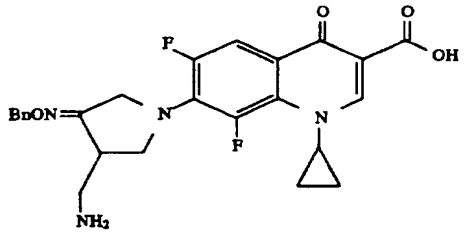
Examples 13 to 22



Examp. No.	R	^{1}H NMR. δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
20		8.6(1H, s), 7.8(1H, d), 7.5(2H, m), 7.2(1H, d), 6.5(1H ,m), 5.0 (2H, m), 4.4(1H, m), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1 (4H, m)	DMSO-d_6	455	4	60
21		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 7.1(3H, m), 6.7(1H, s), 4.4 (1H, m), 3.9(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.3–1.1(4H, m)	DMSO-d_6	541	4	50
22		8.6(1H, s), 8.2(1H, m), 7.9–7.8 (2H, m), 7.4(1H, m), 7.2(1H, d), 5.6(2H, s), 4.4(1H, m), 3.9(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	540	4	70

EXAMPLE 23

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-1 4-dihydro-4-oxo-quinoline-3-carboxylic acid



566 mg of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 584 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile. This suspension was cooled down under ice-water bath and then 913 mg of 1,8-diazabicyclo[5.4.0] undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80° C. and, after adding 10 ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 704 mg (Yield: 73%) of the title compound.

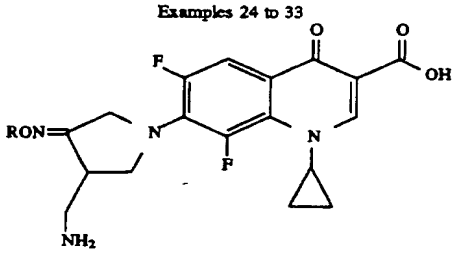
^{1}H NMR (DMSO-d_6, ppm): δ 8.64(1H, s), 7.99(1H, d), 7.41(5H, m), 5.10(2H., s), 4.73(2H, s), 4.18(1H, m), 3.92 (1H, m), 3.86(1H, m), 3.37(2H, m), 3.02(1H, m), 2.83(1H, m), 2.73(1H, m), 1.25–1.05(4H, m); MS (FAB, m/e): 483 (M+H)

EXAMPLES 24 TO 33

The same starting material as Example 23 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 23 to prepare the respective compounds listed in the following Table 10.

TABLE 10

Examples 24 to 33



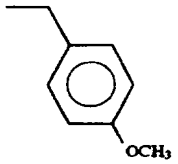
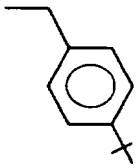
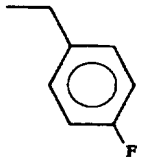
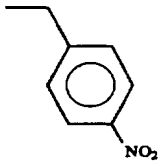
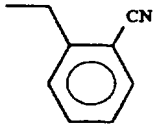
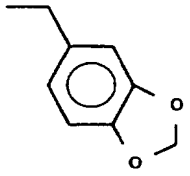
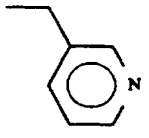
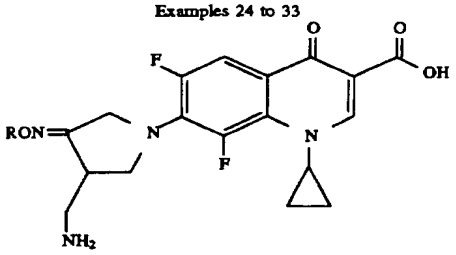
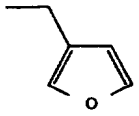
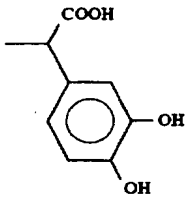
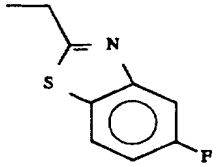
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
24		8.6(1H, s), 7.7(1H, d), 7.2(2H, d), 6.9(2H, d), 5.1(2H, s), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 3.7(3H, s), 2.9(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	513	2	75
25		8.6(1H, s), 7.7(1H, d), 7.5(2H, m), 7.1(2H, m), 5.1(2H, s), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.4(9H, s), 1.15(4H, m)	DMSO-d_6	539	4	70
26		8.6(1H, s), 7.7(1H, d), 7.3(2H, m), 7.1(2H, m), 5.1(2H, s), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	501	4	80
27		8.6(1H, s), 8.2(2H, d), 7.7(1H, d), 7.6(2H, d), 5.3(2H, s), 4.3 (2H, s), 4.1(1H, m,), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	528	3	68
28		8.6(1H, s), 7.9–7.4(5H, m), 5.3 (2H, s), 4.3(2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	508	2	70
29		8.6(1H, s), 7.7(1H, d), 7.0(3H, m), 6.1(2H, s), 5.1(2H, s), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	527	3	69
30		8.6(3H, m), 7.8(1H, d), 7.7(1H, d), 7.4(1H, q), 5.3(2H, s), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	484	3	58

TABLE 10-continued

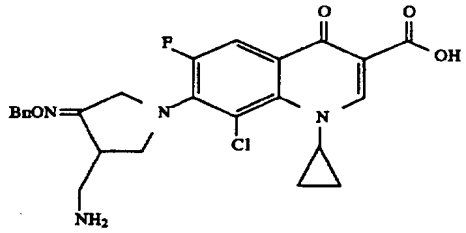
Examples 24 to 33



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
31		8.6(1H, s), 7.7(1H, d), 7.5(2H, m), 6.5(1H, m), 5.0(2H, m), 4.3 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	473	3	70
32		8.6(1H, s), 7.7(1H, d), 7.1(3H, m), 6.6(1H, s), 4.3(2H, s), 4.1 (1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	559	4	59
33		8.6(1H, s), 8.3(1H, m), 7.9(1H, m), 7.7(1H, d), 7.4(1H, m), 5.6 (2H, s), 4.3(2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	558	4	60

EXAMPLE 34

Synthesis of 7-(4-aminomethyl-3-benzyoxyimino-pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-guinoline-3-carboxylic acid



598 mg of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxcquinoline-3-carboxylic acid and 584 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile and then 913 mg of 1,8-diazabicyclo [5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 3 hours at 80° C. and, after adding 15 ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethyl ether to obtain 510 mg (Yield: 52%) of the title compound.

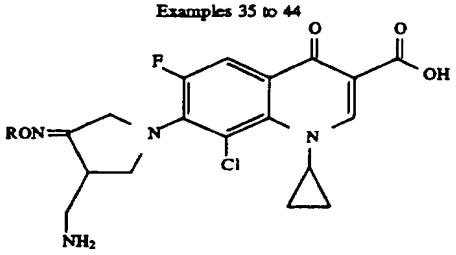
^{1}H NMR (DMSO-d_6, ppm): δ 8.78(1H, s), 7.91(1H, d), 7.41(5H, m), 5.16(2H, s), 4.74(2H, s), 4.16(1H, m), 3.90 (1H, m), 3.85(1H, m), 3.85(2H, m), 3.02(1H, m), 2.82(1H, m), 2.75(1H, m), 1.30–1.10(4H, m); MS (FAB, m/e): 499 (M+H)

EXAMPLES 35 TO 44

The same starting material as Example 34 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 34 to prepare the respective compounds listed in the following Table 11.

TABLE 11

Examples 35 to 44



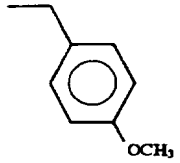
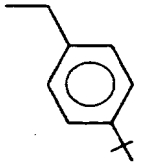
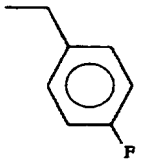
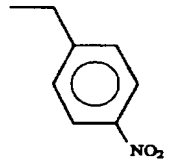
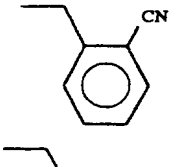
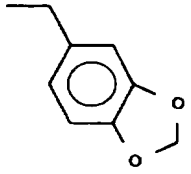
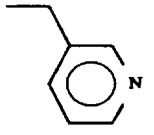
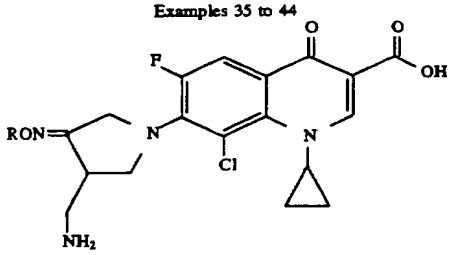
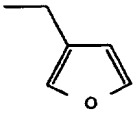
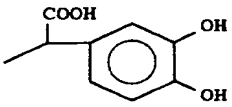
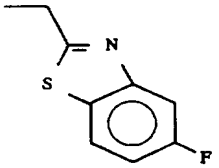
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
35		8.7(1H, s), 7.9(1H, d), 7.3(2H, d), 7.0(2H, d), 5.1(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.7(3H, s), 3.0(1H, m), 2.9–2.6 (2H, s), 1.2–0.9(4H, m)	DMSO-d_6	529	3	63
36		8.7(1H, s), 7.9(1H, d), 7.5(2H, d), 7.3(2H, d), 5.2(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.4 (9H, s), 1.2–0.9(4H, m)	DMSO-d_6	555	3	73
37		8.7(1H, s), 7.9(1H, d), 7.4(2H, m), 7.1(2H, m), 5.1(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	517	2	80
38		8.7(1H, s), 8.3(2H, d), 7.9(1H, d), 7.7(2H, d), 5.4(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	544	4	63
39		8.7(1H, s), 7.9–7.4(5H, m), 5.3 (2H, s), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.2–0.9(4H, m)	DMSO-d_6	524	4	70
40		8.7(1H, s), 7.9(1H, d), 7.0(3H, m), 6.1(2H, s), 5.1(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	543	2	67
41		8.7(1H, s), 7.9(1H, d), 8.6(2H, m), 7.8(1H, d), 7.4(1H, q), 5.2 (2H, s), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.2–0.9(4H, m)	DMSO-d_6	500	4	60

TABLE 11-continued

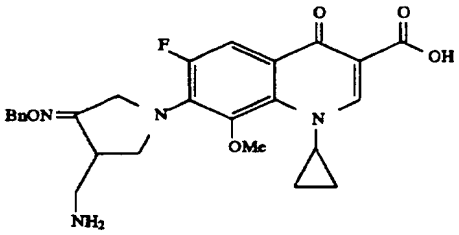
Examples 35 to 44



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
42		8.7(1H, s), 7.9(1H, d), 7.5(2H, m), 6.5(1H, m), 5.0(2H, m), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	489	2	62
43		8.7(1H, s), 7.9(1H, d), 7.1(3H, m), 6.7(1H, s), 4.4(2H, s), 4.3 (1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.6(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	575	4	60
44		8.7(1H, s), 8.2(1H, m), 7.9(2H, m), 7.4(1H, m), 5.6(2H, s), 4.4 (2H, s), 4.3(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	574	4	76

EXAMPLE 45

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



590 mg of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile and then 913 mg of 1,8-diazabicyclo [5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80° C. and, after adding 15 ml of water, was then stirred for 30 minutes at room temperature and filtered. The filtered solid product was washed with water and ethyl ether to obtain 465 mg (Yield: 47%) of the title compound.

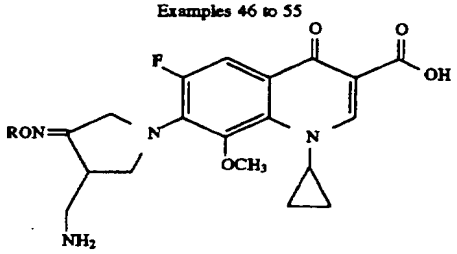
^{1}H NMR (DMSO-d_6, ppm): δ 8.61(1H, s), 7.99(1H, d), 7.40(5H, m), 5.15(2H, s), 4.74(2H, s), 4.17(1H, m), 3.95 (1H, m), 3.83(1H, m), 3.60(3H, s), 3.35(2H, m), 3.02(1H, m), 2.80(1H, m), 2.71(1H, m), 1.30–1.10(4H, m); MS (FAB, m/e): 495(M+H)

EXAMPLES 46 TO 55

The same starting material as Example 45 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 45 to prepare the respective compounds listed in the following Table 12.

TABLE 12

Examples 46 to 55



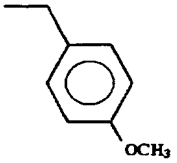
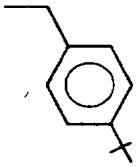
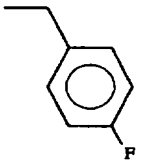
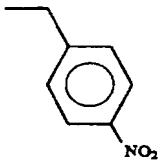
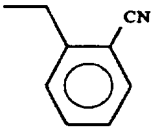
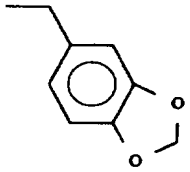
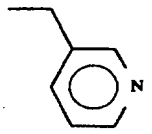
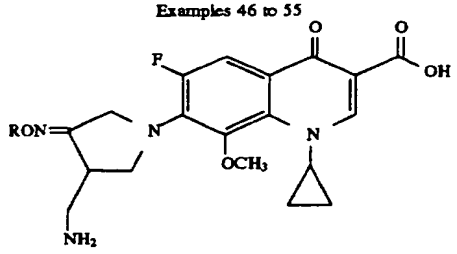
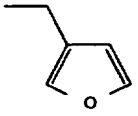
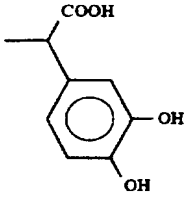
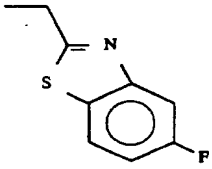
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
46		8.8(1H, s), 7.8(1H, d), 7.4(2H, d), 7.1(2H, d), 5.2(2H, s), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.8(3H, s), 3.0(1H, m), 2.9–2.7(2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	525	17	38
47		8.8(1H, s), 7.8(1H, d), 7.6(2H, d), 7.4(2H, d), 5.3(2H, s), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 1.5(9H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	551	17	34
48		8.8(1H, s), 7.8(1H, d), 7.5(2H, m), 7.2(2H, m), 5.2(2H, s), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	513	17	40
49		8.8(1H, s), 8.3(2H, d), 7.8(1H, d), 7.7(2H, d), 5.4(2H, s), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	540	17	37
50		8.8(1H, s), 8.0–7.5(5H, m), 5.4 (2H, s), 4.6(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9—2.7(2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	520	17	42
51		8.8(1H, s), 7.8(1H, d), 7.0(3H, m), 6.2(2H, s), 5.2(2H, s), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	539	17	44
52		8.8(1H, s), 8.6(2H, m), 7.9(1H, d), 7.8(1H, d), 7.4(1H, q), 5.3 (2H, s), 4.6(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7(2H,m), 2.7(3H, s), 1.3(2H,m), 0.95(2H, m)	DMSO-d_6	496	17	30

TABLE 12-continued

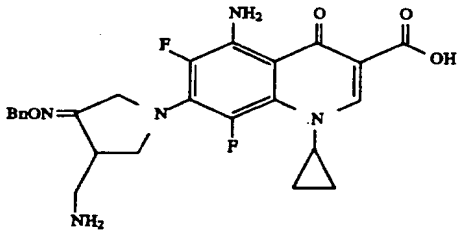
Examples 46 to 55



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
53		8.8(1H, s), 7.8(1H, d), 7.6(2H, m), 6.5(1H, m), 5.1(2H, m), 4.6 (2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	485	17	29
54		8.8(1H, s), 7.8(1H, d), 7.2(3H, m), 6.8(1H, s), 4.6(2H, s), 4.3 (1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.7 (3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	571	20	27
55		8.8(1H, s), 8.3(1H, m), 8.0(1H, m), 7.8(1H, d), 7.5(1H, m), 5.7 (2H, s), 4.6(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.7(3H, s), 1.3(2H, m), 0.95(2H, m)	DMSO-d_6	570	17	42

EXAMPLE 56

Synthesis of 5-amino-7-(4-aminomethyl-3-benzyloxylmino-pyrrolidin-1-yl)-1-cyclopropyl6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



448 mg of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 438 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile and then 685 mg of 1,8-diazabicyclo [5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was heated for 6 hours at 80° C. and 10 ml of water was added thereto. This suspension was filtered. The filtered solid product was washed with water, acetonitrile and ethyl ether to obtain 395 mg (Yield: 53%) of the title compound.

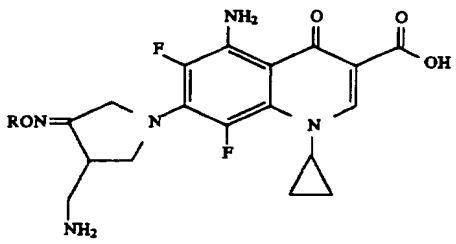
^{1}H NMR (DMSO-d_6, ppm): δ 8.62(1H, s), 7.92(1H, d), 7.40(5H, m), 6.10(2H, bs), 5.13(2H, s), 4.73(2H, s), 4.15 (1H, m), 3.95(1H, m), 3.82(1H, m), 3.35(2H., m), 3.01(1H, m), 2.80(1H, m), 2.73(1H, m), 1.25–1.05(4H, m); MS (FAB, m/e): 498(M+H)

EXAMPLES 57 TO 66

The same starting material as Example 56 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 56 to prepare the respective compounds listed in the following Table 13.

TABLE 13

Examples 57 to 66



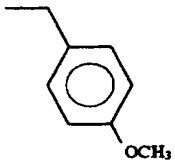
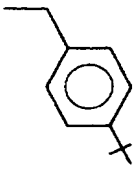
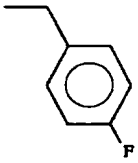
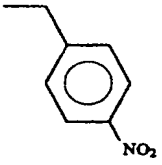
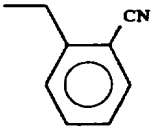
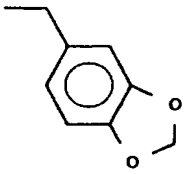
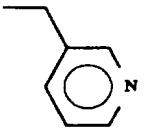
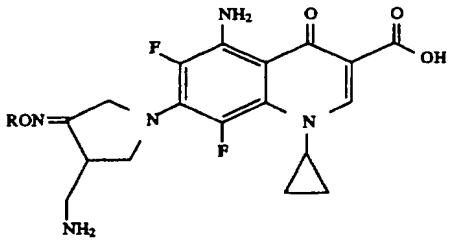
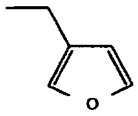
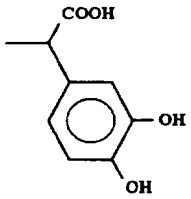
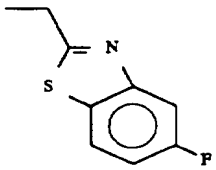
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
57		8.4(1H, s), 7.4(2H, bs), 7.2 (2H, d), 7.0(2H, d), 5.1(2H, s), 4.6(2H, m), 4.2(1H, m), 3.9(1H, m), 3.8(3H, s), 3.7(1H, m), 3.0 (1H, m), 2.8–2.6(2H, m), 1.1 (4H, s)	DMSO-d_6	528	10	59
58		8.4(1H, s), 7.5(2H, d), 7.4(2H, bs), 7.3(2H, d), 5.2(2H, s), 4.6 (2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6 (2H, m), 1.4(9H, s), 1.1(4H, s)	DMSO-d_6	554	17	67
59		8.4(1H, s), 7.4(4H, m), 7.1(2H, m), 5.1(2H, s), 4.6(2H, m), 4.2 (1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.1 (4H, s)	DMSO-d_6	516	17	55
60		8.4(1H, s), 8.2(2H, d), 7.6(2H, d), 7.4(2H, bs), 5.3(2H, s), 4.6 (2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6 (2H, m), 1.1(4H, s)	DMSO-d_6	543	17	56
61		8.4(1H, s), 7.9–7.4(6H, m), 5.3 (2H, s), 4.6(2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.1(4H, s)	DMSO-d_6	523	18	62
62		8.4(1H, s), 7.3(2H, bs), 7.0 (3H, m), 6.2(2H, s), 5.2(2H, s), 4.6(2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.1(4H, s)	DMSO-d_6	542	18	65
63		8.5(3H, m,), 7.6(1H, d), 7.4(1H, q), 7.3(2H, bs), 5.3(2H, s), 4.6 (2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6 (2H, m), 1.1(4H, s)	DMSO-d_6	499	17	52

TABLE 13-continued

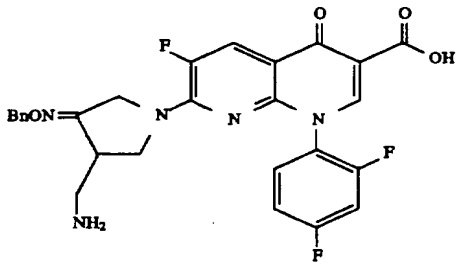
Examples 57 to 66



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
64		8.4(1H, s), 7.5–7.4(4H, m), 6.5 (1H, m), 5.0(2H, m), 4.6(2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.1(4H, s)	DMSO-d_6	488	18	49
65		8.4(1H, s), 7.4(2H, bs), 7.1 (3H, m), 6.7(1H, s), 4.6(2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H), 1.1(4H, s)	DMSO-d_6	574	18	43
66		8.4(1H, s), 8.2(1H, m), 7.9(1H, m), 7.4(3H, m), 5.6(2H, s), 4.6 (2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6 (2H, m), 1.1(4H, s)	DMSO-d_6	573	17	65

EXAMPLE 67

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



806 mg of 7-chloro-1(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 438 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile and then 913 mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for one hour at room temperature, and after adding 15 ml of water, was then stirred for further 30 minutes and filtered. The filtered solid product was washed with water and acetonitrile to obtain 524 mg (Yield: 65%) of the title compound.

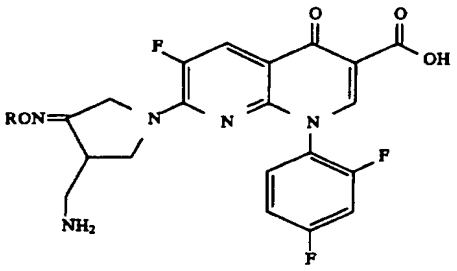
^{1}H NMR (DMSO-d_6, ppm): δ 8.82(1H, s), 8.21(1H, d), 7.85(1H, m), 7.56(1H, m), 7.40(6H, m), 5.16(2H, s), 4.76 (2H, s), 4.18(1H, m), 3.94(1H, m), 3.81(1H, m), 3.34(2H, m), 3.04(1H, m), 2.82(1H, m), 2.73(1H, m), 1.30–1.00(4H, m); MS (FAB, m/e): 538(M+H)

EXAMPLES 68 TO 77

The same starting material as Example 67 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 67 to prepare the respective compounds listed in the following Table 14.

TABLE 14

Examples 68 to 77



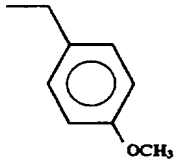
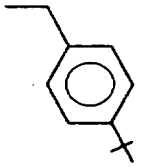
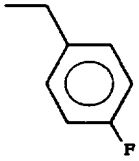
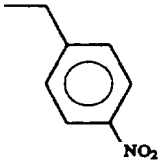
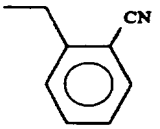
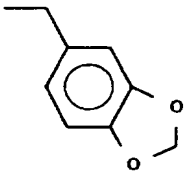
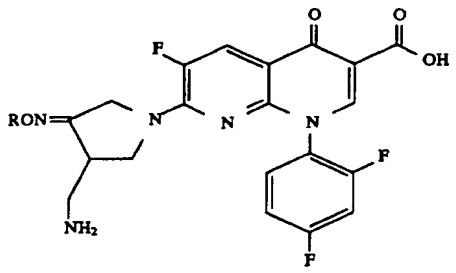
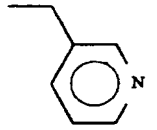
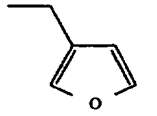
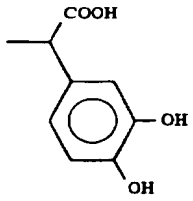
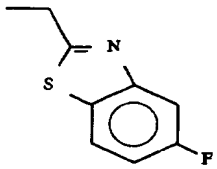
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
68		8.9(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(3H, m), 7.1 (2H, d), 5.2(2H, s), 4.3(2H, s), 4.0(1H, m), 3.9(1H, m), 3.8(3H, s), 3.0(1H, m), 2.8–2.6(2H, m)	DMSO-d_6	568	20	78
69		8.9(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(2H, m), 7.3(2H, m), 5.2 (2H, s), 4.3(2H, s), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.5 (9H, s)	DMSO-d_6	594	10	80
70		8.9(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.4(2H, m), 7.3 (1H, dd), 7.1(2H, m), 5.1(2H, s), 4.3(2H, s), 4.0(1H, m), 3.9 (1H, m), 3.0(1H, m), 2.8–2.6 (2H, m)	DMSO-d_6	556	15	81
71		8.9(1H, s), 8.3(2H, d), 8.1(1H, d), 7.8(1H, m), 7.7(2H, d), 7.6 (1H, dd), 7.3(1H, m), 5.3(2H, s), 4.3(2H, s), 4.0(1H, m, 3.9 (1H, m), 3.0(1H, m), 2.8–2.6 (2H, m)	DMSO-d_6	583	15	75
72		8.8(1H, s), 8.1(1H, d), 7.9–7.4 (6H, m), 7.3(1H, dd), 5.3(2H, s), 4.3(2H, s), 4.0(1H, m), 3.9 (1H, m), 3.0(1H, m), 2.8–2.6 (2H, m)	DMSO-d_6	563	15	80
73		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 7.0(3H, m), 6.2(2H, s), 5.1(2H, s), 4.3(2H, s), 4.0(1H, m), 3.9 (1H, m), 3.0(1H, m), 2.8–2.6 (2H, m)	DMSO-d_6	582	15	87

TABLE 14-continued

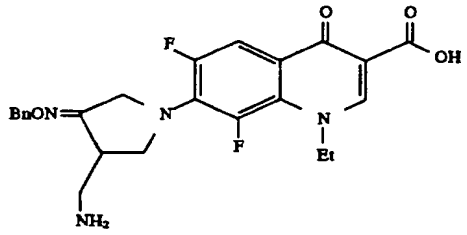
Examples 68 to 77



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
74		8.8(1H, s), 8.6(1H, s), 8.5(1H, q), 7.8(2H, m), 7.6(1H, dd), 7.4 (1H, q), 7.3(1H, dd), 5.2(2H, s), 4.3(2H, s), 4.0(1H, m), 3.9 (1H, m), 3.0(1H, m), 2.8–2.6 (2H, m)	DMSO-d_6	539	15	70
75		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.5(1H, d), 7.45(1H, dd), 6.6(1H, m), 5.0 (2H, m), 4.3(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m)	DMSO-d_6	528	10	69
76		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 7.1(3H, m), 6.7(1H, s), 4.3(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0 (1H, m), 2.8–2.6(2H, m)	DMSO-d_6	614	20	59
77		8.8(1H, s), 8.2(1H, m), 8.1(1H, d), 8.0(1H, m), 7.8(1H, d), 7.6 (1H, dd), 7.4(1H, m), 7.3(1H, dd), 5.6(2H, s), 4.3(2H, s), 4.0 (1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m,)	DMSO-d_6	613	10	82

EXAMPLE 78

Synthesis of 7-(4-aminomethyl-3-benzyloxyiminopyrrolidin-1-yl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



353 mg of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 380 mg of the compound prepared in Preparation 8 were suspended in 15 ml of acetonitrile and then 593 mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2.5 hours at 80° C., and after adding 15 ml of water, was then stirred for further 30 minutes under cold water bath and filtered. The filtered solid product was washed with water, acetonitrile and ethyl ether to obtain 391 mg (Yield: 64%) of the title compound.

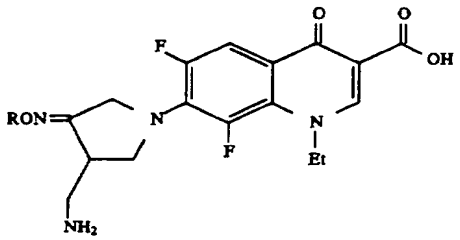
^{1}H NMR (DMSO-d_6, ppm): δ 8.8(1H, s), 7.8(1H, d), 7.40(5H, m), 5.10(2H,s), 4.6(2H, q), 4.4 (2H, dd), 4.0(1H, m), 3.7(1H, m), 3.1(1H, m), 2.8(2H, ddd), 1.46(3H, t); MS (FAB, m/e): 471(M+H)

EXAMPLES 79 TO 88

The same starting material as Example 78 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 78 to prepare the respective compounds listed in the following Table 15.

TABLE 15

Examples 79 to 88



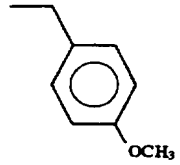
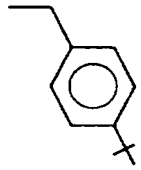
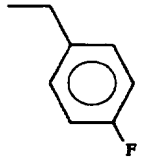
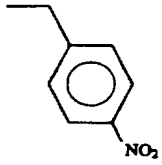
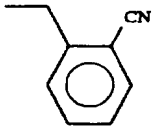
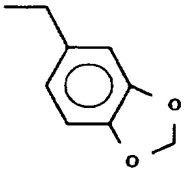
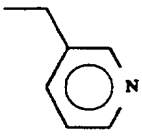
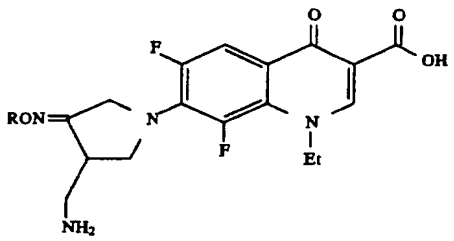
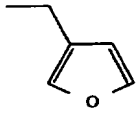
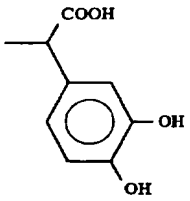
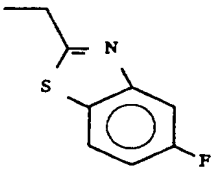
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
79		8.8(1H, s), 7.8(1H, d), 7.4(2H, d), 7.1(2H, d), 5.0(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.7(3H, s), 3.1(1H, m), 2.9–2.7(2H, m), 1.45(3H, t)	DMSO-d_6	501	4	73
80		8.8(1H, s), 7.8(1H, d), 7.4(2H, d), 7.2(2H, d), 5.1(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.1(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t), 1.4(9H, s)	DMSO-d_6	527	2.5	77
81		8.8(1H, s), 7.8(1H, d), 7.3(2H, m), 7.0(2H, m), 5.0(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t)	DMSO-d_6	489	3	80
82		8.8(1H, s), 8.3(2H, d), 7.8(1H, d), 7.7(2H, d), 5.3(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t)	DMSO-d_6	516	3	75
83		8.8(1H, s), 7.9–7.4(5H, m), 5.3 (2H, s), 4.5(2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.45(3H, t)	DMSO-d_6	496	3	80
84		8.8(1H, s), 7.8(1H, d), 6.8(3H, m), 6.0(2H, s), 5.0(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t)	DMSO-d_6	515	4	69
85		8.8(1H, s), 8.6(2H, m), 7.8(2H, m), 7.4(1H, q), 5.3(2H, s), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t)	DMSO-d_6	471	2	70

TABLE 15-continued

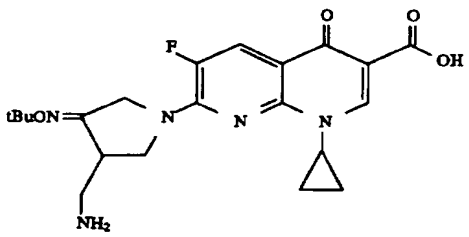
Examples 79 to 88



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
86		8.8(1H, s), 7.8(1H, d), 7.5(2H, m), 6.5(1H, m), 5.0(2H, m), 4.5 (2H, q), 4.4(2H, s), 4.2(1H, m), 2.9(1H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 1.45(3H, t)	DMSO-d_6	461	2	67
87		8.8(1H, s), 7.8(1H, d), 7.1(3H, m), 6.7(1H, s), 4.5(2H, q), 4.4 (2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.45(3H, t)	DMSO-d_6	547	3	63
88		8.8(1H, s), 8.2(1H, m), 7.9(1H, m), 7.8(1H, d), 7.4(1H, m), 5.6 (2H, s), 4.5(2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.5(3H, t)	DMSO-d_6	546	4	70

EXAMPLE 89

Synthesis of 7-(4-aminomethyl-3-t-butyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

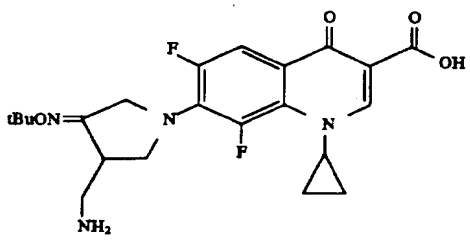


141 mg (0.5 mmole) of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro [1,8]naphthyridine-3-carboxylic acid and 143 mg (0.55 mmole) of 4-aminomethyl-pyrrolidin-3-one t-butyloxime dihydrochloride were thoroughly suspended in 2.5 ml of acetonitrile. Then 230 mg (1.5 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene was slowly added dropwise thereto. The reaction mixture was stirred for 30 minutes at room temperature, and after adding 1 ml of water, was then vigorously stirred for 10 minutes and filtered. The filtered solid product was successively washed with acetonitrile-water (4:1 v/v, 2 ml) and acetoritrile (2 ml×2) and then with ether and dried to obtain 132 mg (Yield: 61%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 8.1(1H, d), 4.6(2H, s), 4.2(1H, dd), 3.9(1H, dd), 3.7(1H, m), 3.1(1H, dd), 2.9–2.7(2H, ddd) 1.3(9H, s), 1.2(2H, m), 1.1(2H, m); FAB MS (POS): 432[M+H]$^+$

EXAMPLE 90

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6, 8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



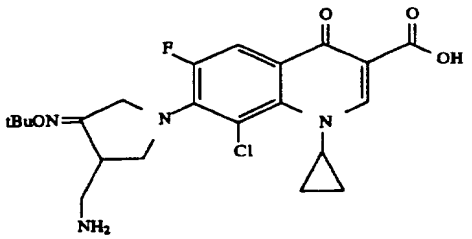
141 mg (0.5 mmole) of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid and 143 mg (0.55 mmole) of 3-aminomethyl-4-t-

butyloxyiminopyrrolidine dihydrochloride were refluxed for 2.5 hours under heating according to the same manner as Example 89 and cooled down to room temperature. Then, the resulting product was then separated and purified with preparative HPLC to obtain 151 mg (Yield: 67%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.3(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.3 (9H, s), 1.5(4H, s); FAB MS(POS): 449[M+H]$^+$

EXAMPLE 91

Synthesis of 8-chloro-1-cycloproyl-6-fluoro-[7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

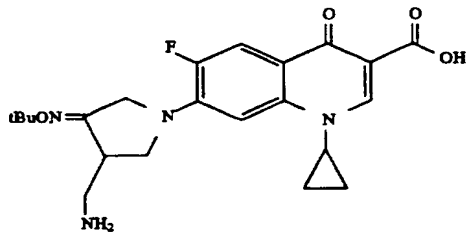


150 mg (0.5 mmole) of 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was reacted according to tho same manner as Example 90. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 148 mg (Yield: 64%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.7(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3(9H, s), 1.2–0.9(4h, m); FAB MS (POS): [M+H]$^+$=465

EXAMPLE 92

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

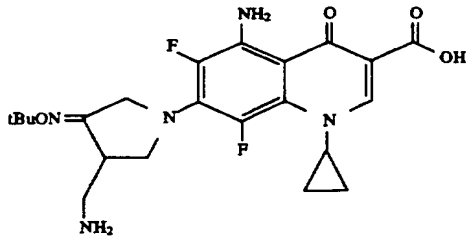


132 mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was refluxed for 3.5 hours under heating according to the same manner as Example 89. Then, the resulting residue was subjected to preparative HPLC to obtain 129 mg (Yield: 60%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 3.9(1H, m), 3.8(1H, m) 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.4(9H, s), 1.3–1.1(4H, m); FAB MS(POS): [M+H]$^+$=431

EXAMPLE 93

Synthesis of 5amino-7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

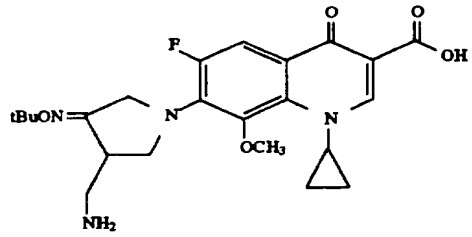


148 mg (0.5 mmole) of 5-amino-1-cyclopropyl-6,7,8-trifluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid was refluxed for 8 hours under heating according to the same manner as Example 89. Then, the resulting residue was purified with preparative HPLC to obtain 151 mg (Yield: 65%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 7.5(2H, br), 4.3(2H, s), 4.0–3.8(3H, m) 3.2(1H, m), 2.8–2.6 (2H, m), 1.3(9H, s), 1.1(4H, m); FAB MS(POS): [M+H]$^+$=464

EXAMPLE 94

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

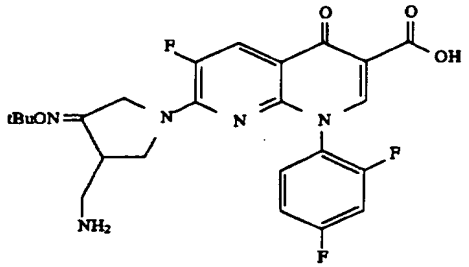


143 mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid was refluxed for 10 hours under heating according to the same manner as Example 89. Then, the resulting residue was purified with preparative HPLC to obtain 92 mg (Yield: 40%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.9(1H, s), 7.8(1H, d), 4.5(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9 (1H, m), 3.0(1H, m), 2.8–2.7(2H, m), 2.7(3H, s), 1.3(9H, s), 1.25(2H, m), 0.9(2H, s); FAB MS(POS): [M+H]$^+$=461

EXAMPLE 95

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-(2, 4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

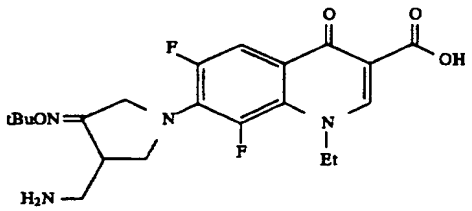


168 mg (0.5 mmole) of 6.7-difluoro-1-(2.4-difluorophenyl)-4-oxo-1. 4-dihydro-naphthyridine-3-carboxylic acid and 143 mg (0.55 mmole) 3-aminomethyl-4-t-butyloxylminopyrrolidine dihydrochloride were suspended in 3 ml of dry acetonitrile. Then. 230 mg (1.5 mmole) of 1.8-diazabicyclo[5.4.0]undec-7-ene was added thereto. and the reaction mixture was stirred for 15 minutes at room temperature and then treated according to the same manner as Example 89 to obtain 203 mg (Yield: 81%) of the title compound.

^{1}H NMR (DMSO-d_6. ppm): δ 8.9(1H. s). 8.1(1H. d). 7.8(1H. m). 7.6(1H. dd). 7.3(1H. dd). 4.3(2H. s). 4.0(1H. m). 3.9(1H. m). 3.0(1H. m). 2.8–2.6(2H. m). 1.3(9H. s); FAB MS(POS): $[M+H]^+$=504

EXAMPLE 96

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-6.8-difluoro-1-ethyl-4 -oxo-1.4-dihydroquinoline-3-carboxylic acid



136 mg (0.5 mmole) of 1-ethyl-6.7.8-trifluoro-4-oxo-1.4-dihydroquinoline-3-carboxylic acid was refluxed for 5 hours under heating according to the same manner as Example 89. Then. the resulting residue was purified with preparative HPLC to obtain 170 mg (Yield: 78%) of the title compound.

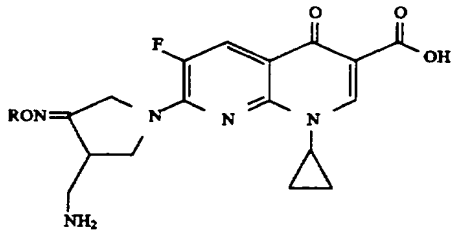
^{1}H NMR (DMSO-d_6. ppm): δ 8.8(1H. s). 7.8(1H. d) 4.5(2H. q). 4.4(2N. s). 4.2(1H. m). 3.9(1H. m). 3.1(1H. m). 2.9–2.7(2H. m). 1.45(3H. t). 1.3(9H. s); FAB MS(POS): $[M+H]^+$=437

EXAMPLES 97 TO 176

The amine compounds prepared in Preparations 41 to 50 were treated according to the same procedure as Examples 89 to 96 to prepare the respective compounds 97 to 176 of which NMR and MS data are listed in the following Tables 16 to 23.

TABLE 16

Examples 97 to 106



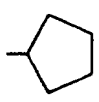
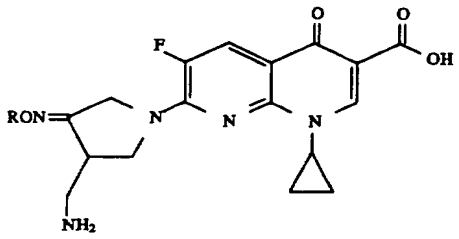
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
97		8.6(1H, s), 8.0(1H, d), 4.7(1H, m), 4.6(2H, s), 4.2(1H, m), 3.9 (1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–1.0(4H, m), 0.9(6H, d)	DMSO-d_6	418	10	73
98		8.6(1H, s), 8.05(1H, d), 4.8 (1H, m), 4.7(2H, s), 4.2(1H, m), 4.0(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.2(2H, m), 2.1(2H, m), 1.7(1H, m), 1.5(1H, m), 1.2–1.0(4H, m)	DMSO-d_6	430	10	63
99		8.6(1H, s), 8.0(1H, d), 4.7(1H, m), 4.5(2H, s), 4.2(1H, m), 3.9 (1H, m), 3.7(1H, m), 3.1(1H, m), 2.9–2.8(2H, m), 1.7(4H, s), 1.6 (2H, m), 1.5(2H, m), 1.2–1.0 (4H, m)	DMSO-d_6	444	50	77

TABLE 16-continued

Examples 97 to 106



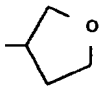
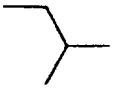
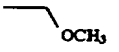
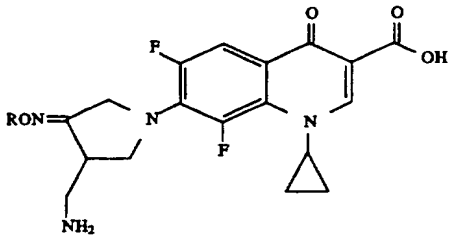
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
100		8.6(1H, s), 8.0(1H, d), 4.8(1H, m), 4.6(2H, s), 4.2(1H, m), 3.9 (1H, m), 3.8–3.6(5H, m), 3.1 (1H, m), 2.9–2.7(2H, m), 2.3–1.9(2H, m), 1.2–1.0(4H, m)	DMSO-d_6	446	30	61
101		8.65(1H, s), 8.05(1H, d), 4.6 (2H, s), 4.25(1H, m), 3.9(1H, m), 3.85(2H, dd), 3.75(1H, m), 3.1(1H, m), 3.0–2.8(2H, m), 1.3–1.0(5H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	430	30	84
102		8.6(1H, s), 8.0(1H, d), 4.6(2H, s), 4.2(1H, m), 3.95(1H, m), 3.8 (2H, d), 3.7(1H, m), 3.05(1H, m), 2.9–2.7(2H, m), 1.9(1H, m), 1.2–1.0(4H, m), 0.9(6H, d)	DMSO-d_6	432	15	80
103		8.60(1H, s), 8.05(1H, d), 4.74 (2H, s), 4.60(2H, s), 4.21(1H, m), 3.97(1H, m), 3.75(1H, m), 3.50(1H, s), 3.35(2H, s), 3.08 (1H, m), 2.90–2.70(2H, m), 1.30–1.05(4H, m)	DMSO-d_6	414	90	63
104		8.6(1H, s), 8.0(1H, d), 4.6(2H, s), 4.2(1H, m), 4.1(2H, t), 3.9 (1H, m), 3.7(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 2.8(1H, s), 2.5 (2H, t), 1.2–1.0(4H, m)	DMSO-d_6	428	15	65
105		8.6(1H, s), 8.0(1H, d), 4.6(2H, s), 4.2(1H, m), 3.9(1H, m), 3.7 (1H, m), 3.4(2H, s), 3.3(3H, s), 3.0(1H, m), 2.8–2.6(2H, m), 1.2–1.0(4H, m)	DMSO-d_6	420	20	52
106		8.6(1H, s), 8.05(1H, d), 4.6 (2H, s), 4.3(2H, t), 4.2(1H, m), 3.9(1H, m), 3.8(2H, t), 3.7(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.2–1.0(4H, m)	DMSO-d_6	438	10	50

TABLE 17

Examples 107 to 116



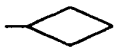
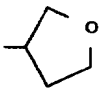
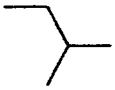
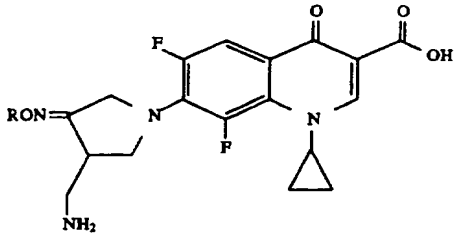
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB. MS (M + 1)	Reac. time (hr)	Yield (%)
107		8.8(1H, s), 7.8(1H, d), 4.7(1H, m), 4.5(2H, s), 4.1(1H, m), 3.9 (1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.15(4H, s), 0.9(6H, d)	DMSO-d_6	435	2	69
108		8.8(1H, s), 7.8(1H, d), 4.8(1H, m), 4.4(2H, s), 4.1(1H, m), 3.9 (1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 2.2(2H, m), 2.1 (2H, m), 1.7(1H, m), 1.5(1H, m), 1.15(4H, s)	DMSO-d_6	447	2	61
109		8.8(1H, s), 7.8(1H, d), 4.7(1H, m), 4.5(2H, s), 4.1(1H, m), 3.9 (1H, m), 3.8(1H, m), 2.9(1H, m), 2.8–2.7(2H, m), 1.7(4H, s), 1.6 (2H, m), 1.5(2H, m), 1.15(2H, m), 1.0(2H, m)	DMSO-d_6	461	2	63
110		8.8(1H, s), 7.8(1H, d), 4.8(1H, m), 4.5(2H, s), 4.1(1H, m), 3.9 (1H, m), 3.8–3.6(4H, m), 3.1 (1H, m), 2.8–2.7(2H, m), 2.3–1.9(2H, m), 1.2–1.0(4H, s)	DMSO-d_6	463	2	54
111		8.8(1H, s), 7.8(1H, d), 4.5 (2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(2H, dd), 3.75(1H, m), 3.1 (1H, m), 2.8–2.7(2H, m), 1.15 (4H, m), 1.05(1H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	447	2	59
112		8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.1(1H, m), 3.9(1H, m), 3.8 (2H, d), 3.75(1H, m), 3.0(1H, m), 2.8–2.7(2H, m), 1.9(1H, m), 1.2–1.0(4H, m), 0.9(6H, d)	DMSO-d_6	449	2	64
113		8.8(1H, s), 7.8(1H, d), 4.62 (2H, s), 4.3(2H, s), 4.1(1H, m), 3.9(1H, m), 3.8(1H, m), 3.5 (1H, s), 2.9(1H, m), 2.8–2.7 (2H, m), 1.15(4H, m)	DMSO-d_6	431	4	55
114		8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.1(1H, m), 4.0(2H, t), 3.9 (1H, m), 3.8(1H, m), 3.1(1H, m), 2.8–2.7(2H, m), 2.7(1H, s), 2.5 (2H, t), 1.2(4H, m)	DMSO-d_6	445	2	65
115		8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.1(1H, m), 3.9(1H, m), 3.8 (1H, m), 3.3(2H, s), 3.1(3H, s), 3.0(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	437	1.5	47

TABLE 17-continued

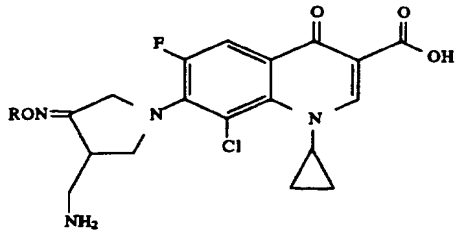
Examples 107 to 116



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
116		8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.3(2H, t), 4.1(1H, m), 3.9 (1H, m), 3.8(2H, t), 3.75(1H, m), 3.0(1H, m), 2.8–2.7(2H, m), 1.15(4H, m)	DMSO-d_6	455	1.5	53

TABLE 18

Examples 117 to 126



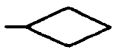
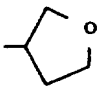
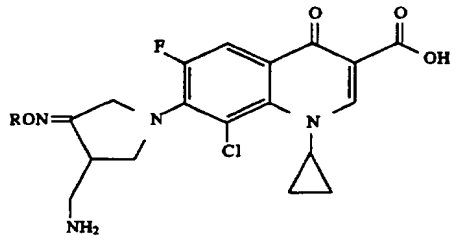
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
117		8.8(1H, s), 7.9(1H, d), 4.7(1H, m), 4.4(2H, s), 4.3(1H, m), 3.8 (1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.8–0.9(4H, m), 0.9(6H, d)	DMSO-d_6	451	2.5	68
118		8.8(1H, s), 7.9(1H, d), 4.7(1H, m), 4.4(2H, s), 4.3(1H, m), 3.8 (1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.2(2H, m), 2.1(2H, m), 1.7(1H, m), 1.5(1H, m), 1.12–0.9(4H, m)	DMSO-d_6	463	2	61
119		8.8(1H, s), 7.9(1H, d), 4.7(1H, m), 4.4(2H, s), 4.3(1H, m), 3.8 (1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.7(4H, s), 1.6 (2H, m), 1.5(2H, m), 1.2–0.9 (4H, m)	DMSO-d_6	477	2	55
120		8.8(1H, s), 7.9(1H, d), 4.8(1H, m), 4.4(2H, s), 4.3(1H, m), 3.8–3.6(6H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 2.3–1.9(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	479	2.5	49
121		8.8(1H, s), 7.9(1H, d), 4.4 (2H, s), 4.3(1H, m), 3.8–3.7 (4H, m), 3.0(1H, m), 2.9–2.7 (2H, m), 1.2–0.9(5H, m), 0.5 (2H, m), 0.3(2H, m)	DMSO-d_6	463	2	52

TABLE 18-continued

Examples 117 to 126



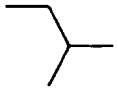
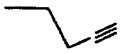
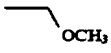
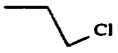
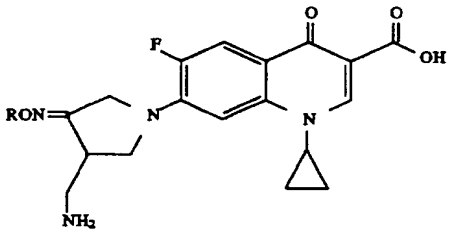
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
122		8.8(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(1H, m), 3.8–3.7(4H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.9(1H, m), 1.2–0.9(4H, m), 0.9(6H, d)	DMSO-d_6	465	2	60
123		8.8(1H, s), 7.9(1H, d), 4.61 (2H, s), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.5(1H, s), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	447	2	62
124		8.8(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(1H, m), 4.1(2H, t), 3.8 (1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.8(1H, s), 2.5 (2H, t), 1.2–0.9(4H, m)	DMSO-d_6	461	2.5	57
125		8.8(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.7 (1H, m), 3.3(2H, s), 3.1(3H, s), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	453	1.5	51
126		8.8(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(3H, m), 3.8–3.7(4H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	471	2	64

TABLE 19

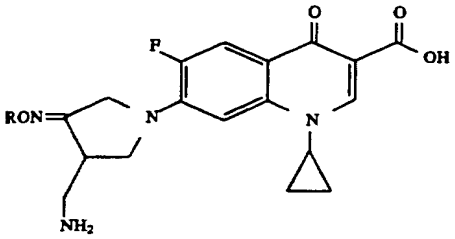
Examples 127 to 136



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
127		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.6(1H, m), 4.4(2H, s), 3.9 (1H, m), 3.8(1H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m), 0.9(6H, d)	DMSO-d_6	417	3	55

TABLE 19-continued

Examples 127 to 136



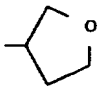
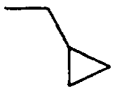
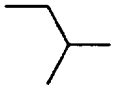
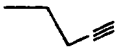
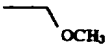
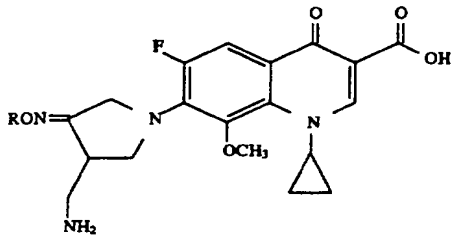
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
128		8.6(1H, s), 7.8(1H, d), 7.2 (1H, d), 4.7(1H, m), 4.4(2H, s), 3.9(1H, m), 3.8(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.2(2H, m), 2.1(2H, m), 1.7(1H, m), 1.5(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	429	3	52
129		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.7(1H, m), 4.4(2H, s), 3.9 (1H, m), 3.8(1H , m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.7 (4H, s), 1.6(2H, m), 1.5(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	443	3	59
130		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.8(1H, m), 4.4(2H, s), 3.9 (1H, m), 3.8–3.6(6H, m), 3.0 (1H, m), 2.9–2.7(2H, m), 2.3–1.9(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	445	3	45
131		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.6(1H, m), 4.4(2H, s), 3.9 (1H, m), 3.8–3.7(3H, m), 3.1 (1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m), 1.0(1H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	429	3	57
132		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 3.9(1H, m), 3.8 (3H, m), 3.7(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.9(1H, m), 1.3–1.1(4H, m), 0.9(6H, d)	DMSO-d_6	431	3	76
133		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.6(2H, s), 4.4(2H, s), 3.9 (1H, m), 3.8(1H, m), 3.7(1H, m), 3.5(1H, s), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	413	3	49
134		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 4.1(2H, t), 3.9 (1H, m), 3.8(1H, m), 3.7(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 2.8(1H, s), 2.5(2H, t), 1.3–1.1(4H, m)	DMSO-d_6	427	3	59
135		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 4.1(2H, t), 3.9 (1H, m), 3.8(1H, m), 3.7(1H, m), 3.3(2H, s), 3.2(3H, s), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1 (4H, m)	DMSO-d_6	419	1.5	47
136		8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 4.3(2H, t), 3.9 (1H, m), 3.8(3H, m), 3.7(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3–1.1(4H, m)	DMSO-d_6	437	2	53

TABLE 20

Examples 137 to 146



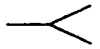
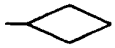
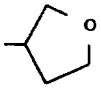
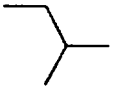
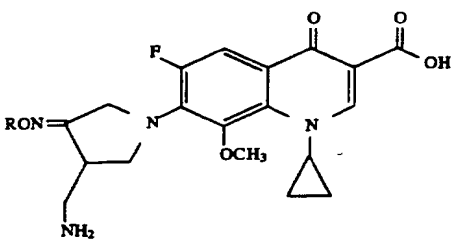
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
137		8.8(1H, s), 7.8(1H, d), 4.7(1H, m), 4.5(2H, s), 4.3(1H, m), 4.1 (1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.7(2H, m), 2.65(3H, s), 1.3(2H, m), 1.0(2H, m), 0.9 (6H, d)	DMSO-d_6	447	9	57
138		8.8(1H, s), 7.8(1H, d), 4.8(1H, m), 4.7(2H, s), 4.3(1H, m), 4.2 (1H, m), 3.9(1H, m), 3.0(1H, m), 2.9–2.7(2H, m), 2.7(3H, s), 2.2 (2H, m), 2.1(2H, m), 1.6(1H, m), 1.5(1H, m), 1.3(2H, m), 0.95 (2H, m)	DMSO-d_6	459	12	65
139		8.8(1H, s), 7.8(1H, d), 4.7(1H, m), 4.5(2H, s), 4.3(1H, m), 4.2 (1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.8(2H, m), 2.7(3H, s), 1.7 (4H, s), 1.6(2H, m), 1.5(2H, m), 1.3(2H, m), 0.9(2H, m)	DMSO-d_6	473	12	63
140		8.8(1H, s), 7.8(1H, d), 4.8(1H, m), 4.6(2H, s), 4.3(1H, m), 4.2 (1H, m), 4.0(1H, m), 3.8–3.6 (4H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 2.7(3H, s), 2.3–1.9 (2H, m), 1.3(2H, m), 0.9(2H, m)	DMSO-d_6	475	12	42
141		8.8(1H, s), 7.8(1H, d), 4.6 (2H, s), 4.3(1H, m), 3.9(1H, m), 3.85(2H, dd), 3.1(1H, m), 3.0–2.8(2H, m), 2.7(3H, s), 1.3(2H, m), 1.1(1H, m), 0.9(2H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	459	12	63
142		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.3(1H, m), 4.2(1H, m), 3.95 (1H, m), 3.8(2H, d), 3.05(1H, m), 2.9–2.7(2H, m), 2.7(3H, s), 1.9(1H, m), 1.3(2H, m), 1.0(2H, m), 0.9(6H, d)	DMSO-d_6	461	12	68
143		8.8(1H, s), 7.8(1H, d), 4.62 (2H, s), 4.60(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.5 (1H, s), 3.0(1H, m), 2.7(3H, s), 2.9–2.7(2H, m), 1.3(2H, m), 1.0(2H, m)	DMSO-d_6	443	12	30
144		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.3(1H, m), 4.2(1H, m), 4.15(2H, t), 3.1(1H, m), 2.9–2.7(2H, m), 2.8(1H, s), 2.7(3H, s), 2.5(3H, t), 1.3(2H, m), 0.9(2H, m)	DMSO-d_6	457	12	52

TABLE 20-continued

Examples 137 to 146



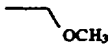
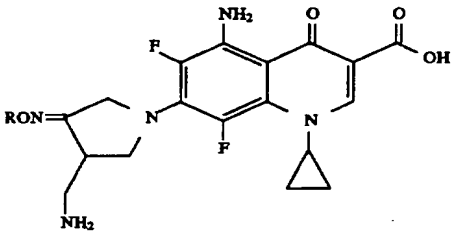
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
145		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.3(1H, m), 4.15(1H, m), 3.9 (1H, m), 3.3(2H, s), 3.1(3H, s), 2.9(1H, m), 2.8–2.6(2H, m), 2.7(3H, s), 1.3(2H, m), 0.9(2H, m)	DMSO-d_6	449	8	39
146		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.3(2H, t), 4.25(1H, m), 4.2 (1H, m), 3.9(1H, m), 3.8(2H, t), 2.9–2.7(2H, m), 2.7(3H, s), 1.3 (2H, m), 1.0(2H, m)	DMSO-d_6	467	12	57

TABLE 21

Examples 147 to 156



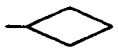
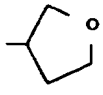
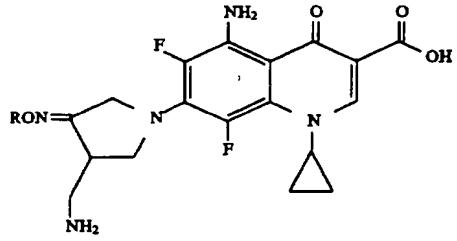
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
147		8.4(1H, s), 7.7(2H, br), 4.5 (1H, m), 4.3(2H, s), 4.0–3.8 (3H, m), 3.2(1H, m), 2.8–2.6 (2H, m), 1.1(4H, s), 0.9 (6H, d)	DMSO-d_6	450	5	73
148		8.3(1H, s), 7.3(2H, br), 4.8 (1H, m), 4.3(2H, s), 4.0–3.8 (3H, m), 2.8–2.6(2H, m), 2.2 (2H, m), 2.1(2H, m), 1.6(1H, m), 1.5(1H, m), 1.1(4H, m)	DMSO-d_6	462	8	64
149		8.4(1H, s), 7.4(2H, br), 4.7 (1H, m), 4.5(2H, s), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 1.7(4H, s), 1.6(2H, m), 1.5(2H, m), 1.1 (4H, m)	DMSO-d_6	476	8	61
150		8.4(1H, s), 7.4(2H, br), 4.8 (1H, m), 4.6(2H, s), 4.2(1H, m), 4.0(1H, m), 3.8–3.6(4H, m), 3.0(1H, m), 2.8–2.6(2H, m), 2.3–1.9(2H, m), 1.2–0.9(4H, m)	DMSO-d_6	478	12	54

TABLE 21-continued

Examples 147 to 156



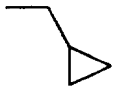
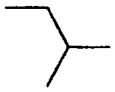
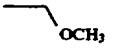
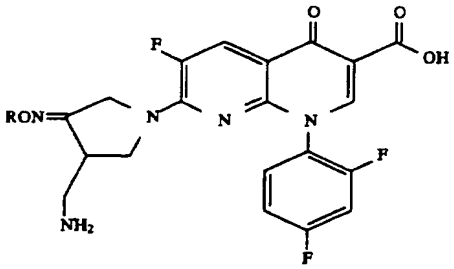
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
151		8.4(1H, s), 7.5(2H, br), 4.6 (2H, s), 3.9(1H, m), 3.8(2H, dd), 3.0(1H, m), 2.9–2.8(2H, m), 1.0(1H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	462	5	82
152		8.4(1H, s), 7.5(2H, br), 4.5 (2H, s), 3.9(1H, m), 3.8(2H, dd), 3.1(1H, m), 2.9–2.7(2H, m), 1.9(1H, m), 1.2–1.1(4H, m), 0.9(6H, d)	DMSO-d_6	464	6	75
153		8.4(1H, s), 7.4(2H, br), 4.6 (2H, s), 4.59(2H, m), 4.2(1H, m), 3.9(1H, m), 3.7(1H, m), 3.5 (1H, s), 3.0(1H, m), 2.8–2.6 (2H, m), 1.1(4H, s)	DMSO-d_6	446	4	50
154		8.4(1H, s), 7.5(2H, br), 4.4 (2H, s), 4.1(1H, m), 4.0(2H, t), 3.9(1H, m), 3.8(1H, m), 3.1(1H, m), 2.8–2.7(2H, m), 2.8(1H, s), 2.5(2H, t), 1.2–0.9(4H, m)	DMSO-d_6	460	5	70
155		8.4(1H, s), 7.4(2H, br), 4.4 (2H, s), 4.3(2H, t), 4.1(1H, m), 3.9(1H, m), 3.7(2H, t), 3.6(1H, m), 3.3(2H, s), 3.0(3H, s), 2.9 (1H, m), 2.8–2.6(2H, m), 1.3–0.9(4H, m)	DMSO-d_6	452	3	60
156		8.4(1H, s), 7.4(2H, br), 4.4 (2H, s), 4.3(2H, t), 4.0(2H, m), 3.9(1H, m), 3.8(2H, t), 3.7(1H, m), 3.2(1H, m), 2.9–2.7(2H, m), 1.1(4H, s)	DMSO-d_6	470	5	72

TABLE 22

Examples 157 to 166



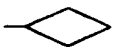
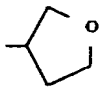
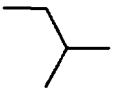
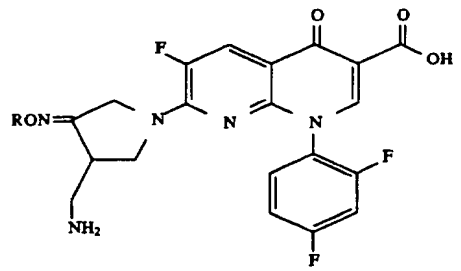
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
157		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.6(1H, m), 4.3(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 0.9(6H, d)	DMSO-d_6	490	15	64
158		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.7(1H, m), 4.4(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 2.2(2H, m), 2.1(2H, m), 1.7(1H, m), 1.5(1H, m)	DMSO-d_6	502	20	61
159		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.7(1H, m), 4.4(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 2.2(2H, m), 2.1(2H, m), 1.7(1H, m), 1.5(1H, m)	DMSO-d_6	516	35	70
160		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.8(1H, m), 4.4(2H, s), 4.0(1H, m), 3.9(1H, m), 3.8–3.6(4H, m), 3.0(1H, m), 2.9–2.6(2H, m), 2.3–1.9(2H, m)	DMSO-d_6	518	35	55
161		8.8(1H, s), 8.1(1H, d), 7.8 (1H, dd), 7.6(1H, dd), 7.3(1H, dd), 4.6(2H, s), 4.2(1H, m), 3.9(1H, m), 3.8(2H, dd), 3.0 (1H, m), 2.8–2.6(2H, m), 1.1 (1H, m), 0.5(2H, m), 0.3(2H, m)	DMSO-d_6	502	30	65
162		8.8(1H, s), 8.1(1H, d), 7.8(1H, dd), 7.6(1H, dd), 7.3(1H, dd), 4.6(2H, s), 4.0(1H, m), 3.9(1H, m), 3.8(2H, d), 3.0(1H, m), 2.8–2.6(2H, m), 1.9(1H, m), 0.9(6H, d)	DMSO-d_6	504	20	70
163		8.79(1H, s), 8.01(1H, d), 7.8 (1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.73(2H, s), 4.61(2H, s), 4.21(1H, m), 3.75(1H, m), 3.50 (1H, s), 3.35(2H, s), 3.08(1H, m), 2.90–2.70(2H, m)	DMSO-d_6	486	60	52
164		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.6(2H, s), 4.1(1H, m), 4.0(2H, t), 3.9(1H, m), 3.0(1H, m), 2.8–2.6(2H, m), 2.7(1H, s), 2.5(2H, t)	DMSO-d_6	500	25	53

TABLE 22-continued

Examples 157 to 166



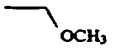
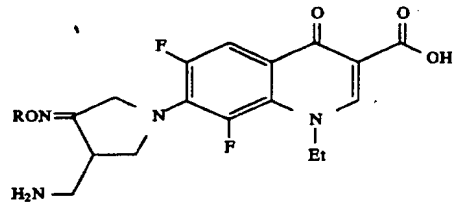
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (min)	Yield (%)
165		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.6(2H, s), 4.1(1H, m), 3.9(1H, m), 3.3(2H, s), 3.1(3H, s), 3.0 (1H, m), 2.8–2.6(2H, m)	DMSO-d_6	492	30	47
166		8.8(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, m), 4.6 (2H, s), 4.3(2H, t), 4.1(1H, m), 3.9(1H, m), 3.8(2H, t), 3.1(1H, m), 2.8–2.6(2H, m)	DMSO-d_6	510	15	51

TABLE 23

Examples 167 to 176



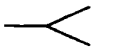
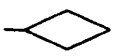
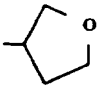
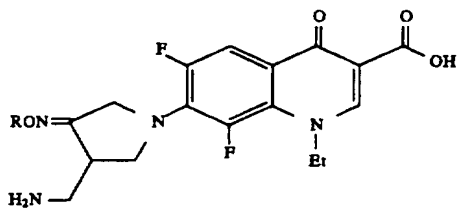
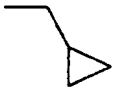
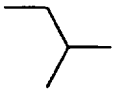
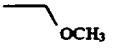
Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
167		8.8(1H, s), 7.8(1H, d), 4.6(1H, m), 4.5(2H, q), 4.4(2H, s), 4.2 (1H, m), 3.9(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 1.45(3H, t), 0.9(6H, d)	DMSO-d_6	423	4.5	82
168		8.8(1H, s), 7.8(1H, d), 4.7(1H, m), 4.5(2H, q), 4.4(2H, s), 4.2 (1H, m), 4.1(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 2.2(2H, m), 2.1 (2H, m), 1.7(1H, m), 1.6(1H, m), 1.45(3H, t)	DMSO-d_6	435	5	73
169		8.8(1H, s), 7.8(1H, d), 4.75 (1H, m), 4.6(2H, s), 4.5(2H, q), 4.2(1H, m), 3.9(1H, m), 3.0–2.7 (2H, m), 1.8(4H, s), 1.65(2H, s), 1.5(2H, s), 1.4(3H, t)	DMSO-d_6	449	5	77
170		8.7(1H, s), 7.8(1H, d), 4.8(1H, m), 4.55(2H, s), 4.5(2H, dd), 4.15(1H, m), 3.85(1H, m), 3.7 (2H, m), 3.1(1H, m), 2.9–2.7 (2H, m), 2.1–1.9(2H, m), 1.5 (3H, t)	DMSO-d_6	451	6	71

TABLE 23-continued

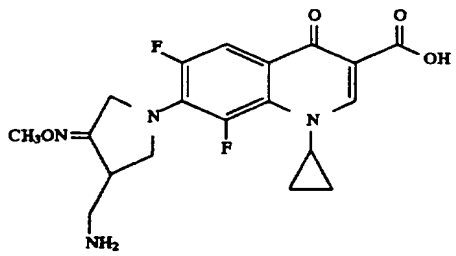
Examples 167 to 176



Examp. No.	R	^{1}H NMR, δ (ppm)	NMR solv.	FAB, MS (M + 1)	Reac. time (hr)	Yield (%)
171		8.8(1H, s), 7.8(1H, d), 4.6 (2H, s), 4.45(2H, m), 4.25(1H, m), 3.9(2H, dd), 3.7(1H, m), 3.1(1H, m), 1.45(3H, t), 0.5 (2H, m), 0.25(2H, m)	DMSO-d_6	435	5	84
172		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.5(2H, q), 4.2(1H, m), 3.9 (1H, m), 3.85(2H, dd), 3.1(1H, m), 2.9–2.7(2H, m), 1.9(1H, m), 0.9(6H, d)	DMSO-d_6	437	4	70
173		8.8(1H, s), 7.8(1H, d), 4.62 (2H, s), 4.5(2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.5(1H, s), 3.1(1H, m), 2.9–2.7(2H, m), 1.45(3H, t)	DMSO-d_6	419	3	50
174		8.8(1H, s), 7.8(1H, d), 4.5(2H, dd), 4.2(1H, m), 4.15(2H, t), 3.9(1H, m), 3.1(1H, m), 2.9–2.7(2H, m), 2.8(1H, s), 2.5(2H, t), 1.5(3H, t)	DMSO-d_6	433	4.5	72
175		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.5(2H, dd), 4.15(1H, m), 3.9(1H, m), 3.3(2H, s), 3.1(3H, s), 2.9(1H, m), 2.8(1H, m), 2.6 (1H, m), 1.5(3H, t)	DMSO-d_6	425	2	39
176		8.8(1H, s), 7.8(1H, d), 4.6(2H, s), 4.5(2H, dd), 4.3(2H, t), 4.2 (1H, m), 3.9(1H, m), 3.8(2H, t), 2.9–2.7(2H, m), 1.5(3H, t)	DMSO-d_6	443	2	57

EXAMPLE 177

Synthesis of 7-(4-amino-3-methoxylmino-pyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

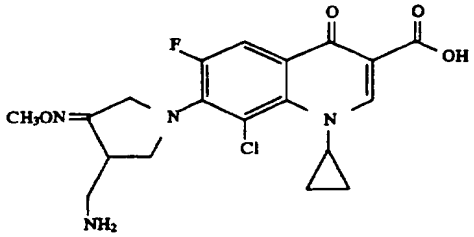


2.83 g (10 mmole) of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid and 4.27 g (11.5 mmole) of 4-aminomethyl-pyrrolidin-3-one O-methyloxime ditrifluoroacetate were added to 23 ml of dry acetonitrile. Then, 4.6 g (30 mmole) of 1,8-diazabicyclo [5.4.0]undec-7-ene was added thereto and the mixture was refluxed for 1.5 hours under heating and then cooled down to room temperature. 15 ml of distilled water was added to the reaction solution. The precipitated solid product was separated and dried to obtain 2.24 g (Yield: 55%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 7.75(1H, d), 4.35(2H, s), 4.1–3.9(2H, m), 3.8(3H, s), 3.7(1H, m), 3.35 (1H, m), 2.9–2.6(2H, m), 1.25 (2H, d), 0.95(2H, s); FAB MS (POS): [M+H]=407

EXAMPLE 178

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-8-chloro-1-cycloprooyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

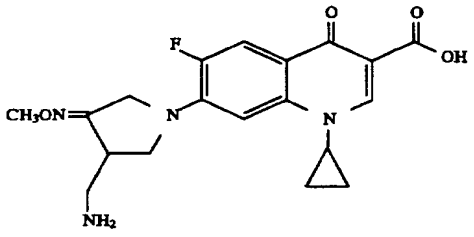


141 mg (0.5 mmole) of 1-cyclopropyl-8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205 mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for one hour according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 88 mg (Yield: 42%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.7(1H, s), 7.85(1H, d), 4.4(1H, m), 3.75(3H, s), 3.7(3H, m), 3.4(2H, m), 3.0–2.7 (2H, m), 1.25(2H, d), 1.0(2H, s); FAB MS(POS): [M+H]= 423

EXAMPLE 179

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopronyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

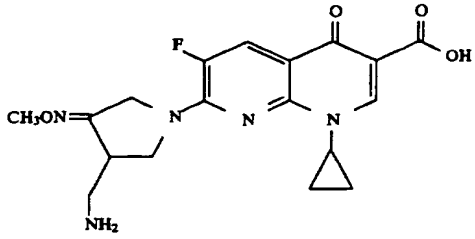


132 mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205 mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 3 hours according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 73 mg (Yield: 37%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 7.85(1H, d), 7.2(1H, d), 4.4(2H, d), 3.9(1H, m), 3.85(3H, s), 3.8–3.65 (2H, m), 3.0(1H, m), 2.9–2.7(2H, m), 1.3(2H, m), 1.1(2H, m); FAB MS(POS): [M+H]=389

EXAMPLE 180

Synthesis of 7-(4-aminomethyl-3-methoxyiminonyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8] naphthyridine-3-carboxylic acid

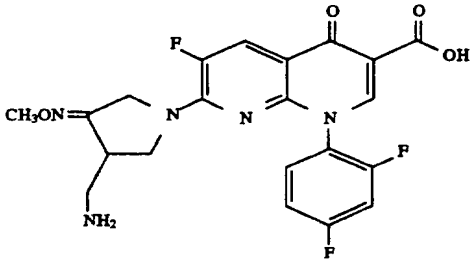


141 mg (0.5 mmole) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro [1,8]naphthyridine-3-carboxylic acid and 205 mg (0.5 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 0.5 hour according to the same manner as Example 177 to obtain 167 mg (Yield: 85%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.6(1H, s), 8.05(1H, d), 4.55(2H, s), 4.3(1H, m), 3.85(3H, s, 1H, m), 3.7 (1H, m), 3.1–3.0(2H, m), 1.2–1.0(4H, m); FAB MS(POS): [M+H]= 390

EXAMPLE 181

Synthesis of 7-(4-aminomethyl-3-methoxylminonyrrolidin-1-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydror [1,8]naphthyridine-3-carboxylic acid

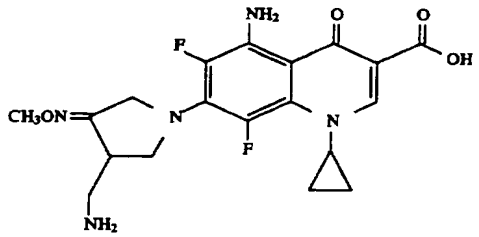


177 mg (0.5 mmole) of 1-(2,4-difluorophenyl)-7-chloro-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 205 mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 0.5 hour according to the same manner as Example 177 to obtain 59 mg (Yield: 25%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm): δ 8.85(1H, s), 8.05(1H, d), 7.75(1H, dd), 7.6(1H, dd), 7.35(1H, dd), 4.3(2H, m), 3.8(3H, s, 1H, m), 3.6(1H, m), 3.0 (1H, m), 2.7(2H, m); FAB MS(POS): [M+H]=462

EXAMPLE 182

Synthesis of 1-cyclopropyl-5-amino-6,8-difluoro-7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-4-oxo-1 4-dihydroquinoline-3-carboxylic acid



148 mg (0.5 mmole) of 1-cyclopropyl-5-amino-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205 mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluorcacetate were refluxed for 4 hours under heating according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 84 mg (Yield: 40%) of the title compound.

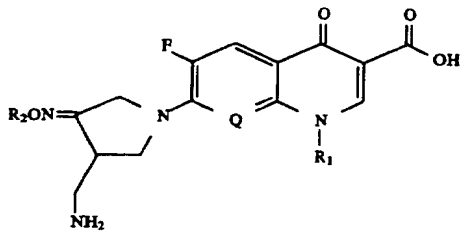
^{1}H NMR (DMSO-d_6, ppm): δ 8.49(1H, s), 7.28(2H, bs), 4.3(2H, s), 3.9(2H, m), 3.8(3H, s), 3.7(1H, m), 2.6–2.8(3H, m), 1.05(4H, m); FAB MS(POS): $[M+H]^+$=422

EXAMPLES 183 TO 202

The compounds prepared in Preparations 40 and 55 to 57 were treated according to the same procedure as Example 177 to 182 to prepare the respective compounds 183 to 202 of which NMR and MS data are listed in the following Table 24.

TABLE 24

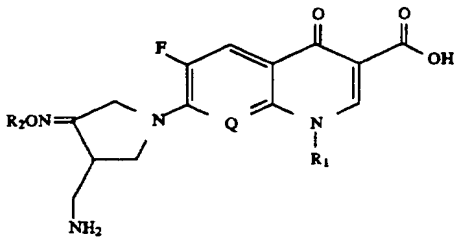
Examples 183 to 202



Ex. No.	Q	R_1	R_2	^{1}H NMR (DMSO-d_6) δ (ppm)	FAB MS (POS) [M + H]	Reac. Time (hr)	Yield (%)
183	CF		H	8.8(1H, s), 7.9(1H, d), 4.35(1H, m), 3.8(2H, m), 3.7(2H, m), 3.4 (1H, m), 3.0(2H, m), 1.2–1.0 (4H, m)	393	2.5	41
184	CF		Et	8.8(1H, s), 7.9(1H, d), 4.4(1H, m), 4.2(2H, q), 4.1–3.9(2H, m), 3.4(2H, m), 2.8(2H, m), 1.4(3H, t), 1.25–1.0(4H, m)	421	2	38
185	CF		Ph	8.8(1H, s), 7.9(1H, d), 7.3–7.1 (5H, m), 4.3(1H, m), 3.9–3.7(3H, m), 3.4(2H, m), 2.8(2H, m), 1.2 (2H, d), 1.05(2H, s)	469	4	29
186	CF		tBu	8.8(1H, s), 7.9(1H, d), 4.35(1H, d), 4.1–3.9(3H, m), 3.4(2H, m), 2.9–2.7(2H, m), 1.35(9H, s), 1.2–0.95(4H, m)	449	2	35
187	CCl		H	8.9(1H, s), 7.9(1H, d), 4.4(1H, m), 3.8(2H, m), 3.7(2H, m), 3.4 (1H, m), 2.9(2H, m), 1.25(2H, m), 1.1(2H, s)	409	1.5	39
188	CCl		Et	8.9(1H, s), 7.9(1H, d), 4.35 (1H, m), 4.2(2H, q), 3.95–3.75 (3H, m), 3.7(2H, m), 3.4(2H, m), 2.85–2.7(2H, m), 1.4(3H, t), 1.3–1.15(4H, m)	437	1.5	37
189	CCl		Ph	8.9(1H, s), 7.9(1H, d), 7.3–7.1 (5H, m), 4.35(1H, m), 4.1–3.9 (3H, m), 3.65(2H, m), 3.35(2H, m), 2.8–2.7(2H, m), 1.15(2H, d), 0.95(2H, s)	485	4.5	25
190	CCl		tBu	8.9(1H, s), 7.85(1H, d), 4.3(1H, m),3.95–3.8(3H, m), 3.7(2H, m), 3.4(2H, m), 2.8(2H, m), 1.3(9H, s), 1.2–1.0(4H, m)	465	3	51

TABLE 24-continued

Examples 183 to 202



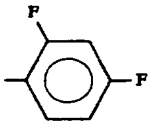
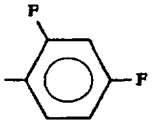
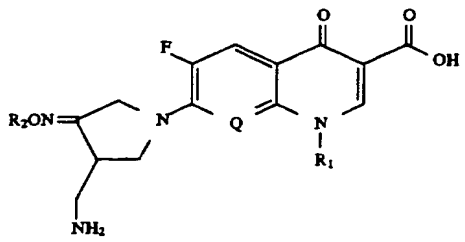
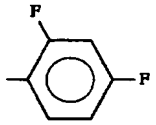
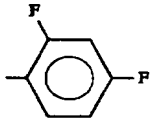
Ex. No.	Q	R_1	R_2	^{1}H NMR (DMSO-d_6) δ (ppm)	FAB MS (POS) [M + H]	Reac. Time (hr)	Yield (%)
191	CH		H	8.6(1H, s), 7.85(1H, d), 7.2(1H, d), 4.4(1H, m), 3.9(2H, m), 3.8–3.65(3H, m), 2.9–2.7(2H, m), 1.3 (2H, d), 1.1(2H, s)	375	2.2	42
192	CH		Et	8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(1H, m), 4.25(2H, q), 3.9–3.7(3H, m), 3.5(2H, m), 2.9–2.7 (2H, m), 1.3(3H, t), 1.25–0.95 (4H, m)	403	1.5	40
193	CH		Ph	8.6(1H, s), 7.8(1H, d), 7.5–7.2 (5H, m, 1H, d), 4.35(1H, m), 4.0–3.8(3H, m), 3.5(2H, m), 2.85–2.7 (2H, m), 1.3(2H, d), 1.15(2H, s)	451	4.5	31
194	CH		tBu	8.6(1H, s), 7.75(1H, d), 7.2(1H, d), 4.35(1H, m), 4.0–3.8(3H, m), 3.5(2H, m), 2.9–2.7(2H, m), 1.4 (9H, s), 1.2–1.05(4H, m)	431	3	43
195	N		H	8.6(1H, s), 8.1(1H, d), 4.5(2H, s), 4.3(1H, m), 3.8(1H, m), 3.65 (1H, m), 3.35(1H, m), 3.0–2.9 (2H, m), 1.2–1.0(4H, m)	376	1	61
196	N		Et	8.6(1H, s), 8.05(1H, d), 4.55 (2H, s), 4.3(1H, m), 4.25(2H, q), 3.8(1H, m), 3.7(1H, m), 3.4 (1H, m), 3.0–2.85(2H, m), 1.35 (3H, t), 1.2–0.95(4H, m)	404	1	57
197	N		Ph	8.6(1H, s), 8.1(1H, d), 7.7–7.3 (5H, m), 4.6(2H, s), 4.35(1H, m), 3.9(1H, m), 3.75(1H, m), 3.4(1H, m), 3.05–2.8(3H, m), 1.25(2H, d), 1.05(2H, s)	452	1	40
198	N		tBu	8.6(1H, s), 8.05(1H, d), 4.55 (2H, s), 4.35(1H, m), 3.95(1H, m), 3.7(1H, m), 3.35(1H, m), 3.0–2.85(2H, m), 1.35(9H, s), 1.15 (2H, d), 1.0(2H, s)	432	1.5	54
199	N		H	8.85(1H, s), 8.1(1H, d), 7.75 (1H, m), 7.6(1H, dd), 7.35(1H, dd), 4.3(1H, m), 3.8(3H, m), 3.6 (1H, m), 3.0(1H, m), 2.7(2H, m)	448	1	33
200	N		Et	8.85(1H, s), 8.05(1H, d), 7.75 (1H, m), 7.6(1H, dd), 7.35(1H, dd), 4.3(1H, m), 4.25(2H, q), 3.75(3H, m), 3.6(2H, m), 2.95 (2H, m), 2.7–2.6(2H, m), 1.4 (3H, t)	476	1	37

TABLE 24-continued

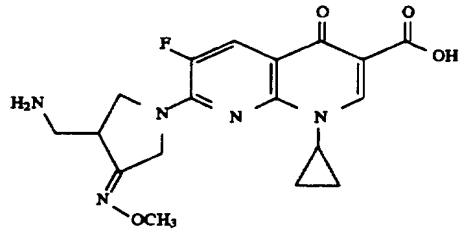
Examples 183 to 202



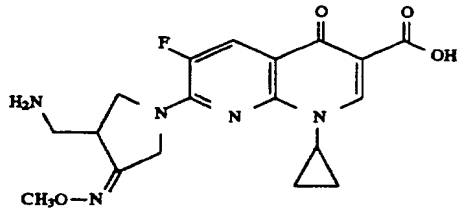
Ex. No.	Q	R_1	R_2	^{1}H NMR (DMSO-d_6) δ (ppm)	FAB MS (POS) [M + H]	Reac. Time (hr)	Yield (%)
201	N		Ph	8.85(1H, s), 8.1(1H, d), 7.75 (1H, m), 7.6(1H, dd), 7.55–7.35 (5H, m, 1H, dd), 4.35(1H, m), 3.75 (3H, m), 3.65(2H, m), 3.0(2H, m), 2.85(2H, m)	524	1.5	29
202	N		tBu	8.85(1H, s), 8.05(1H, d), 7.75 (1H, m), 7.55(1H, dd), 7.3(1H, dd), 4.3(1H, m), 3.8(3H, m), 3.55 (2H, m), 2.9(2H, m), 2.7–2.65 (2H, m), 1.3(9H, s)	504	0.5	41

EXAMPLE 203

Separation of E, Z Isomer of the Compound Prepared in Example 180



Z-isomer (anti)



E-isomer (syn)

3.99 g (10 mmol) of the 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid prepared in Example 180 was completely dissolved in 100 ml of a solvent mixture of dichloromethane and methanol (9/1, v/v), under reflux. 1.0 g (10.5 mmol) of methanesulfonic acid was added thereto in one portion while stirring. The resulting solution was heated overnight. After the heated solution was cooled to −10° C., it was filtered. The filtrate was twice washed with 10 ml of methanol, then washed with 20 ml of diethylether, and finally dried under nitrogen flow to obtain 3.6 g (Yield 75%) of a beige cake containing oxime Z/E mixture (80:20 on HPLC).

E-isomer: t_R=6.64 min

Z-isomer: t_R=8.37 min

250 mg of the powder thus obtained was dissolved in 3 ml of water and the resulting solution was separated on Preparative HPLC. The desired fraction was collected and readily adjusted to about pH 6.5 by adding 1 N NaOH. After the acetonitrile was evaporated, the resulting suspension was filtered and washed with water (2 ml×3). The wet cake thus obtained was extracted with chloroform (20 ml×2). The remaining solvent was evaporated and the residue was dried in vacuo to obtain 30 mg of white solid. The E- and Z-isomers were collected using the same procedure.

E-isomer

^{1}H NMR($CDCl_3$, δ, ppm): 8.69(1H,s), 8.05(1H,d,J=12.5 Hz), 4.60(2H,dd,J=19 Hz), 4.12(2H,dd,J=8 Hz), 4.00(3H,s), 3.71(1H,m), 3.55(1H,m), 3.10(2H,d), 1.36(2H,m), 1.14(2H, m)

Z-isomer($CDCl_3$, δ, ppm): 8.70(1H,s), 8.05(1H,d), 4.61 (2H,s), 4.28(1H,dd), 3.99(3H,s), 3.90(1H,m), 3.69(1H,m), 3.10(1H,m), 3.00(2H,d), 1.30(2H,,), 10.5(2H,m)

EXAMPLE 204

Synthesis of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

3.89 g (10 mmol) of 7-(4-aminomethyl-3-methyloxyminopyrrolidin-1 -yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid prepared as in Example 180 was suspended in 110 ml of a solvent mixture of dichloromethane and ethanol (8/2, v/v). 0.94 g (9.8 mmol) of methanesulfonic acid was added dropwise thereto and the resulting solution was thoroughly stirred for 1 hour at 0° C. The solid thus produced was

filtered, washed with ethanol, and then dried to obtain 4.55 g of the title compound. m.p.: 195° C. (dec.)

^{1}H NMR(DMSO-d_6) δ (ppm): 8.57(1H.s), 8.02(1H.d)

EXAMPLE 205

Synthesis of 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1.8-naphthyridine-3-carboxylic acid methanesulfonate·3 hydrate

A sonicator filled with water was adjusted to 40° C. and was sealed with a lid. Then, a nitrogen introducing tube and a nitrogen excreting tube were connected to the vessel. When the pressure of the dried nitrogen introduced through the nitrogen introducing tube was adjusted to 20 psi, the relative humidity of the humidified nitrogen excreted through the excreting tube was more than 93%. 1 g of the anhydride having moisture content of about 2.5% prepared in Example 204 was introduced into a fritted filter and the humidified nitrogen prepared according to the above mentioned process was passed through. Samples were taken after 0, 5, 10, 20, 30, and 60 minutes, respectively, and the moisture content with the lapse of time was measured. From the results shown in FIG. 8, it can be seen that moisture content of about 10% is constantly maintained when the humidifying procedure is carried out over 30 minutes. The X-ray diffraction pattern of the humidified sample was identical to that the 3 hydrate obtained after recrystallization.

EXAMPLE 206

Synthesis of 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1 -yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1.8-naphthyridine-3-carboxylic acid methanesulfonate·1.5 hydrate

The title compound can be prepared by two different processes.

In the first process, 1.0 g of the anhydride prepared in Example 204 was dissolved in 17 ml of a mixture of water and acetone (10/7, v/v). The solvent was slowly evaporated in darkness leaving 0.8 g of the title compound as a solid.

In the second process, 5.0 g of the anhydride prepared in Example 204 was added to 10 ml of water and the mixture was heated to about 45° C. in order to dissolve the anhydride. After 20 ml of ethanol was added thereto, the resulting solution was stirred and then allowed to stand to form a solid. The solid thus produced was filtered and dried under nitrogen flow to obtain 2.6 g of the title compound.

BIOLOGICAL EXAMPLE 1

In Vitro Antibacterial Activity Test

The antibacterial activity of the compounds according to the present invention was determined by measuring their minimum inhibitory concentrations (MIC, μg/ml), against standard strains, clinically isolated strains and strains resistant to some antibacterial agents. In this test, the known antibacterial compounds, ofloxacin and ciprofloxacin, were used as the comparative agents. The minimum inhibitory concentration could be determined by diluting the test compounds according to a two-times dilution method, dispersing the diluted test compounds in Mueller-Hinton agar medium and then inoculating 5 μl of the standard strain having 10^7 CFU per ml to the medium, which is then incubated for 18 hours at 37° C. The measured results are described in the following Table 25.

TABLE 25

Minimum Inhibitory Concentration of the test compounds (μg/ml)

Test Strains	Examples 1	12	34	56	89
Staphylococcus aureus 6538p	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Staphylococcus aureus giorgio	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Staphylococcus aureus 77	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Staphylococcus aureus 241	2	1	4	2	1
Staphylococcus epidermidis 887E	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Staphylococcus epidermidis 178	2	0.5	2	2	0.5
Streptococcus faecalis 29212	0.031	0.031	0.13	0.016	0.063
Bacillus subtilis 6633	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Micrococcus luteus 9341	0.063	0.13	0.13	0.063	0.25
Escherichia coli 10536	≦0.008	≦0.008	0.016	≦0.008	0.016
Escherichia coli 3190Y	≦0.008	0.016	≦0.008	≦0.008	0.016
Escherichia coli 851E	0.016	0.063	0.13	≦0.008	0.063
Escherichia coli TEM3 3455E	0.25	0.5	1	0.5	0.25
Escherichia coli TEM5 3739E	0.063	0.25	0.5	0.25	0.13
Escherichia coli TEM9 2639E	0.063	0.25	0.13	0.063	0.063
Pseudomonas aeruginosa 1912E	1	2	0.5	2	2
Pseudomonas aeruginosa 10145	2	0.5	2	2	2
Acinetobacter calcoaceticus 15473	≦0.008	0.016	0.031	≦0.008	0.031
Citrobacter diversus 2046E	0.063	0.13	0.25	0.016	0.13
Enterobacter cloacae 1194E	0.031	0.13	0.25	0.031	0.13
Enterobacter cloacae P99	≦0.008	0.063	0.063	≦0.008	0.016
Klebsiella aerogenes 1976E	0.25	1	0.5	0.5	0.5
Klebsiella aerogenes 1082E	0.063	0.13	0.031	0.016	0.25
Salmonella typimurium 14028	0.13	0.25	0.063	0.031	0.13

Test Strains	Examples 97	102	103	104	177
Staphylococcus aureus 6538p	≦0.008	0.016	≦0.008	≦0.008	≦0.008
Staphylococcus aureus giorgio	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Staphylococcus aureus 77	0.016	0.016	≦0.008	≦0.008	0.016
Staphylococcus aureus 241	2	4	4	8	0.5
Staphylococcus epidermidis 887E	≦0.008	≦0.008	≦0.008	0.016	≦0.008
Staphylococcus epidermidis 178	1	1	4	4	1
Streptococcus faecalis 29212	0.063	0.063	0.031	0.031	0.031
Bacillus subtilis 6633	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Micrococcus luteus 9341	0.063	0.063	0.13	0.13	0.063
Escherichia coli 10536	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Escherichia coli 3190Y	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008
Escherichia coli 851E	0.031	0.063	≦0.008	≦0.008	0.031
Escherichia coli TEM3 3455E	0.13	0.5	0.13	0.25	0.25
Escherichia coli TEM5 3739E	0.063	0.25	0.063	0.13	0.13
Escherichia coli	0.031	0.063	0.031	0.031	0.063

TABLE 25-continued

	Minimum Inhibitory Concentration of the test compounds (μg/ml)				
TEM9 2639E					
Pseudomonas aeruginosa 1912E	1	2	0.5	1	0.5
Pseudomonas aeruginosa 10145	1	2	0.5	1	0.5
Acinetobacter calcoaceticus 15473	0.016	0.063	0.031	≦0.008	0.13
Citrobacter diversus 2046E	0.063	0.13	0.13	≦0.008	0.031
Enterobacter cloacae 1194E	0.063	0.25	0.016	≦0.008	0.063
Enterobacter cloacae P99	≦0.008	0.031	≦0.008	0.016	0.016
Klebsiella aerogenes 1976E	0.25	0.5	0.063	0.13	0.13
Klebsiella aerogenes 1082E	0.13	0.25	0.031	0.031	0.063
Salmonella typimurium 14028	0.13	0.25	0.031	0.031	0.063

	Examples				
Test Strains	178	179	180	OFLX	CFLX
Staphylococcus aureus 6538p	0.031	≦0.008	≦0.008	0.25	0.13
Staphylococcus aureus giorgio	0.016	0.016	≦0.008	0.25	0.25
Staphylococcus aureus 77	0.031	0.031	≦0.008	0.25	0.25
Staphylococcus aureus 241	1	2	2	64	64
Staphylococcus epidermidis 887E	0.031	0.016	≦0.008	0.25	0.13
Staphylococcus epidermidis 178	1	2	2	32	128
Streptococcus faecalis 29212	0.063	0.031	0.063	2	0.5
Bacillus subtilis 6633	0.016	≦0.008	≦0.008	0.063	0.031
Micrococcus luteus 9341	0.25	0.13	0.13	2	2
Escherichia coli 10536	0.031	<0.008	≦0.008	0.031	≦0.008
Escherichia coli 3190Y	0.016	≦0.008	≦0.008	0.016	≦0.008
Escherichia coli 851E	0.063	≦0.008	≦0.008	0.063	0.016
Escherichia coli TEM3 3455E	1	0.13	0.25	0.5	0.25
Escherichia coli TEM5 3739E	0.5	0.063	0.13	0.5	0.13
Escherichia coli TEM9 2639E	0.25	0.031	0.031	0.063	0.031
Pseudomonas aeruginosa 1912E	0.5	0.25	0.25	0.5	0.31
Pseudomonas aeruginosa 10145	1	0.25	0.25	2	0.25
Acinetobacter calcoaceticus 15473	0.13	0.016	0.0634	0.25	0.25
Citrobacter diversus 2046E	0.13	0.031	0.016	0.063	0.016
Enterobacter cloacae 1194E	0.13	0.031	0.031	0.063	0.031
Enterobacter cloacae P99	0.063	0.008	≦0.008	≦0.008	≦0.008
Klebsiella aerogenes 1976E	0.5	0.13	0.13	0.25	0.13
Klebsiella aerogenes 1082E	0.25	0.031	0.016	0.063	≦0.008
Salmonella typimurium 14028	0.063	0.063	0.031	0.13	0.031

Note)
OFLX = Ofloxacin
CFLX = Ciprofloxacin

BIOLOGICAL EXAMPLE 2

Pharmacokinetic Test

The pharmacokinteic property parameters of the compounds of the present invention were determined using SD rats (male), weighing about 230±10 g. Specifically, the test compounds of the present invention were administered in an amount of 20 mg/kg of body weight to test rats via femoral veins. Then, bloods were collected at certain intervals after administration of the test compounds from femoral veins and analyzed by means of Agar Well Method to measure the blood concentration of the test compounds from which pharmacokinetic parameters, half life ($T_{1/2}$), and AUC (area under the curve), were calculated. The obtained results are described in the following Table 26.

TABLE 26

		Pharmacokinetic parameters			
	Route	$T_{1/2}$ (hr)	C_{max} (μg/ml)	T_{max} (hr)	F (%)
CFLX	IV	1.76 ± 0.035			71
	PO	1.7 ± 0.108	1.34 ± 0.368	1.13 ± 0.605	
EX. 89	IV	2.29 ± 1.13			>100
	PO	6.69 ± 2.78	4.89 ± 2.23	2.18 ± 0.77	
EX. 177	IV	1.92 ± 0.38			47.23
	PO	3.93 ± 1.31	0.37 ± 0.11	0.51 ± 0.33	

Note:
CFLX = Ciprofloxacin
IV = Intravenous
PO = Per oral
$T_{1/2}$ = Biological half life
C_{max} = Maximum blood concentration
T_{max} = Time showing maximum blood concentration after administration of the test compound
F = Bioavailability

BIOLOGICAL EXAMPLE 3

Acute Oral Toxicity Test

To determine the acute oral toxicity of the compounds prepared in Examples 1 and 34, the test solution containing the compounds in various concentrations were orally administered to ICR male mouse in an amount of 10 ml per kg of body weight. For 7 days after administration, the lethality and the conditions of test mouse were observed, from which LD_{50} value (mg/kg), was calculated. The obtained results are described in the following Table 27.

TABLE 27

Toxicity	
Test Compound (Example No.)	LD_{50} value (mg/kg)
1	>3,000
34	>3,000

TEST EXAMPLE 1

Moisture Adsorption Test of the Anhydride Prepared in Example 204

Under various relative humidities at 25° C., the moisture adsorption velocity and the equilibrium moisture content of the anhydride prepared in Example 203 were determined by means of an automatic moisture adsorption analyzer (MB 300 G Gravimetric Sorption Analyzer). This instrument produces a specific relative humidity at a specific temperature and continuously records the weight change of a sample due to adsorption or desorption of moisture as measured by a micro balance inside the instrument. 16 mg of the anhydride sample was loaded on the micro balance and the moisture contained in the sample was removed under a dry nitrogen stream at 50° C. A weight change of less than 5 μg per 5 minutes was the criterion for complete dryness.

Thereafter, the inner temperature was adjusted to 25° C., and the sample was tested varying the relative humidity from 0 to 95% at 5% intervals. The sample was considered to have reached equilibrium at each relative humidity tested when the weight change was less than 5 μg per 5 minutes. FIG. 1 shows the moisture adsorption velocity, that is, the time required for the sample to reach equilibrium at each relative humidity from 0 to 95% at 5% intervals. Initial moisture adsorption proceeded very speedily at each relative humidity tested. In most cases, the equilibrium was reached within 2 hours. FIG. 2 shows the weight increment(%) at each relative humidity, that is, the equilibrium moisture content. It is clear from FIG. 2 that the equilibrium moisture content is dependent upon the relative humidity.

TEST EXAMPLE 2

Thermal Analysis of the Anhydride Prepared in Example 204 and 3 Hydrate Prepared in Example 205

For the Differential Scanning Calorimetry, METTLER TOLEDO DSC821e and METTLER TOLEDO STARe System were used. 3.7 mg of sample was weighed into the aluminum pan, which was then press sealed with an aluminum lid. After three tiny needle holes were made on the lid, the sample was tested by heating from normal temperature to 250° C. at a rate of 10° C./min. As can be seen from FIG. 9, the endothermic peak due to the vaporization of the water molecules contained in the 3 hydrate begins at around 50° C. and the exothermic peak due to the thermal decomposition was observed at around 180° to 220° C. In contrast, the anhydride showed only an exothermic peak due to thermal decomposition at around 185° to 220° C. without any endothermic peak.

In the thermogravimetric analysis, SEIKO TG/DTA220 was used. 3.8 mg of the sample was weighed into an aluminum pan and was heated from normal temperature to 250° C. at a rate of 10° C./min according to the temperature raising program. As can be seen from FIG. 10, weight decrement was observed at the temperature range of endothermic peak, the extent of which corresponds to the moisture content determined by Karl-Fisher method (Mettler Toledo DL37KF Coulometer).

TEST EXAMPLE 3

Equilibrium Moisture Content Determination of Hydrates

Six saturated aqueous salt solutions were introduced into each desiccator to control the inner relative humidity to a specific value as represented in the following Table 28. Then, equilibrium moisture contents of 3 hydrate and 1.5 hydrate prepared in Examples 205 and 206, respectively, were determined at several relative humidities.

TABLE 28

Saturated salt solutions inside the desiccator

Salt Solution	Relative Humidity (%) at 25° C.
Potassium Acetate	23
Magnesium Chloride	33
Potassium Carbonate	43
Magnesium Nitrate	52
Sodium Nitrite	64
Sodium Chloride	75

Specifically, 100 mg of the sample was spread on a preweighed Petri dish and the total weight was accurately measured, then three of the sample were placed in each desiccator of Table 28. The desiccators were allowed to stand at normal temperature for 7 days and then the sample was taken to be weighed. After 13 days had passed, one of the three samples inside each desiccator was taken and the moisture content of each was measured by the thermogravimetric analysis described in Test Example 2. Equilibrium moisture content at each relative humidity is represented in FIG. 3 (3 hydrate), and FIG. 4 (1.5 hydrate). FIG. 3 shows that moisture content of the 3 hydrate is maintained around 10% for the whole relative humidity range tested; FIG. 4 shows that the moisture content of the 1.5 hydrate is maintained around 5% at the relative humidity of 23 to 64%. Both hydrates are stable since they keep a constant equilibrium moisture content regardless of the relative humidity change.

TEST EXAMPLE 4

X-ray Diffraction Analysis

After 50 mg of the anhydride in Example 204, the 3 hydrate in Example 205, and the 1.5 hydrate in Example 206 were each thinly spread on the sample holder. X-ray diffraction analyses (35 kV×20 mA Rigaku Gergeflex D/max-IIIC) were performed under the conditions listed below.

scan speed (2θ) 5°/min

sampling time: 0.03 sec

scan mode: continuous

2θ/θ reflection

Cu-target (Ni filter)

Results of X-ray diffraction analyses on the anhydride, the 3 hydrate, and the 1.5 hydrate were as depicted in FIG. 5, 6, and 7, respectively. From these spectra it can be verified that their crystal forms differ from each other.

TEST EXAMPLE 5

Chemical Stability Under Heating

The chemical stability of both the 3 hydrate prepared in Example 205 and the 1.5 hydrate prepared in Example 206 were compared with the chemical stability of the anhydride prepared in Example 204 as follows in order to determine the effect on chemical stability of the extent of hydration.

The anhydride and each of the hydrates was introduced into a glass vial and maintained at 70° C. Then, the extent of decomposition with elapsed time was analyzed by liquid chromatography and the results thus obtained are described in the following Table 29.

TABLE 29

Thermal stability with elapsed time (at 70° C.)

(Unit: %)

Sample	Time (week) Initial	1	2	3	4
Anhydrate	99	—	97	—	95
3 hydrate	97	—	—	—	94
1.5 hydrate	100	97.25	95.80	97.16	96.17

As can be from Table 29, the 3 hydrate and the 1.5 hydrate both showed the same degree of thermal stability as the anhydride.

TEST EXAMPLE 6

Water Solubility of the Compound Prepared in Example 204

Water solubilities of various salts of the compound, including that of the methanesulfonate prepared in Example 204, were measured. The measurement results are listed in the following Table 30.

TABLE 30

Sample	Water Solubility: Phosphate buffered solution (pH 7)	Phosphate buffered solution (pH 2)
Free form	0.007	14.6
Tartarate	6.7	15.4
Sulfurate	11.4	8.9
p-Toluenesulfonate	7.5	6.8
Methanesulfonate	>30	>20

As can be seen from the above results, the methanesulfonate shows a water solubility superior to that of the tartarate, the sulfurate, and the p-toluenesulfonate as well as the free form. Therefore, it is identified that the methanesulfonate has a desirable solubility as well as an excellent antibacterial activity.

BIOLOGICAL EXAMPLE 4

In Vitro Antibacterial Activity Test

In order to determine the antibacterial activitiers of the E- and Z-isomner of the compound 180 which were separated in Example 203, and of 7- (4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate prepared in Example 204, in vitro antibacterial activities of them were measured using agar medium dilution method. The results were as described in the following Tables 31 and 32. In Table 32, the minimum inhibitory concentration (MIC, μg/ml), was simply calculated in the ratio of weight without considering the molecular weight, and ciprofloxacin was chosen as the control. From the results, it is identified that the Z-isomer has a superior antibacterial activity to the E-isomer and that the methanesulfonate as well as the free form has an excellent antibacterial activity.

TABLE 31

In vitro Antibacterial activity (Minimum Inhibitory Concentration: MIC, μg/ml)

Test Strains	E-isomer	Z-isomer	Ciprofloxacin
Staphylococcus aureus 6538p	0.063	≤0.008	0.13
Staphylococcus aureus giorgio	0.063	≤0.008	0.13
Staphylococcus aureus 77	0.063	0.031	0.25
Staphylococcus aureus 241	16	4	64
Staphylococcus epidermidis 887E	0.031	≤0.008	0.063
Staphylococcus epidermidis 178	32	4	128
Streptococcus faecalis 29212	0.25	0.063	1
Bacillus subtilis 6633	0.031	≤0.008	0.031
Micrococcus luteus 9341	0.5	0.13	2
Escherichia coli 10536	0.031	≤0.008	0.016
Escherichia coli 3190Y	0.016	≤0.008	≤0.008
Escherichia coli 851E	0.063	0.016	≤0.008
Escherichia coli TEM3 3455E	0.5	0.13	0.25
Escherichia coli TEM5 3739E	0.5	0.13	0.13
Escherichia coli TEM9 2639E	0.13	0.031	0.016
Pseudomonas aeruginosa 1912E	1	0.5	0.25
Pseudomonas aeruginosa 10145	2	0.5	0.25
Pseudomonas aeruginosa 6065Y	32	8	4
Acinetobacter calcoaceticus 15473	0.25	0.063	0.25
Citrobacter diversus 2046E	0.13	0.031	0.031
Enterobacter cloacae 1194E	0.13	0.031	0.016
Enterobacter cloacae P99	0.031	≤0.008	≤0.008
Klebsiella aerogenes 1976E	0.25	0.063	0.13
Klebsiella aerogenes 1082E	0.13	0.031	0.016
Proteus vulgaris 6059	1	0.25	0.031
Serratis marsecence 1826E	0.5	0.25	0.063
Salmonella thypimurium 14028	0.13	0.031	0.031

TABLE 32

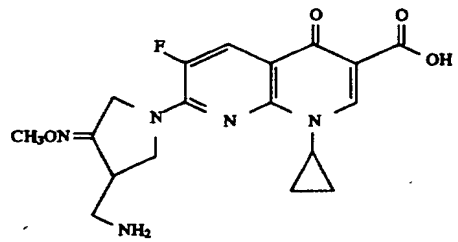
In vitro Antibacterial activity (Minimum Inhibitory Concentration: MIC, μg/ml)

Test Strains	Methanesulfonic acid salt	Ciprofloxacin
Staphylococcus aureus 6538p	0.016	0.13
Staphylococcus aureus giorgio	0.016	0.13
Staphylococcus aureus 77	0.031	0.25
Staphylococcus aureus 241	4	128
Staphylococcus epidermidis 887E	0.016	0.013
Staphylococcus epidermidis 178	4	128
Streptococcus faecalis 29212	0.13	0.5
Bacillus subtilis 6633	0.016	0.031
Micrococcus luteus 9341	0.13	2
Escherichia coli 10536	0.008	<0.008
Escherichia coli 3190Y	0.008	<0.008
Escherichia coli 851E	0.016	<0.008
Escherichia coli TEM3 3455E	0.25	0.5
Escherichia coli TEM5 3739E	0.13	0.13
Escherichia coli TEM9 2639E	0.031	0.016
Pseudomonas aeruginosa 1912E	0.25	0.13
Pseudomonas aeruginosa 10145	0.5	0.5
Acinetobacter calcoaceticus 15473	0.031	0.25
Citrobacter diversus 2046E	0.031	0.016
Enterobacter cloacae 1194E	0.031	0.016
Enterobacter cloacae P99	0.016	<0.008
Klebsiella aerogenes 1976E	0.13	0.13
Klebsiella aerogenes 1082E	0.031	0.016
Proteus vulgaris 6059	0.25	0.031
Serratis marsecence 1826E	0.13	0.063
Salmonella thypimurium 14028	0.031	0.031

Although this invention has been described in its preferred form with a certain degree of particularity, it is appreciated by those skilled in the art that the present disclosure of the preferred form has been made only by way of example and that numerous changes in the details of the construction, combination and arrangement of parts may be resorted to without departing from the spirit and scope of the invention.

What is claimed is:

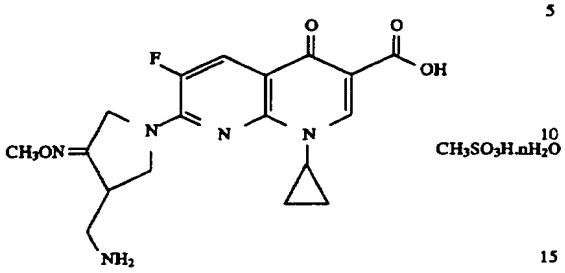
1. 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-1,8-naphthyridine-3-carboxylic acid represents by the following formula:



or a pharmaceutically acceptable non-toxic salt, physiologically hydrolyzable ester, or isomer thereof.

2. The compound according to claim 1 in the from of the Z isomer.

3. 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof represented by the following formula:



or its isomer, in which n denotes 0, 1, 1.5, 2, 2.5, 3, 3.5 or 4; or an isomer thereof.

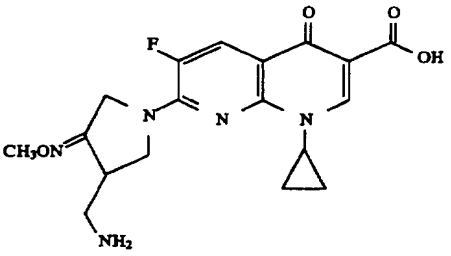
4. The compound according to claim 3, wherein n is 3.

5. The compound according to claim 3, which has a moisture content of from 9 to 11% by weight.

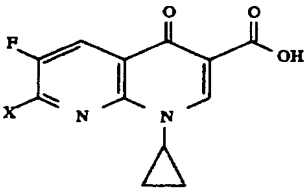
6. The compound according to claim 3, wherein n is 1.5.

7. The compound according to claim 3, which has a moisture content of from 4 to 6% by weight.

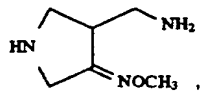
8. A process for preparing 7-(4-aminomethyl-3-methyloxylminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid represented by the following formula:



or its isomer, methanesulfonate and hydrate of the methanesulfonate, which comprises reacting a quinolone compound represented by the following formula,



in which X represents a halogen, with a pyrrolidine oxime compound represented by the following formula, or a salt thereof.



in a solvent in the presence of an acid acceptor.

9. The process of claim 8, wherein the ratio of the number of moles of the pyrrolidine oxime compound to the number of moles of the quinolone compound ranges from one(1), to ten(10).

10. The process of claim 8, wherein said solvent is selected from the group consisting of acetonitrile, dimethylformamide, dimethylsulfoxide, pyridine, N-methylpyrrolidinone, hexamethylphosphoramide, ethanol, and aqueous mixtures thereof .

11. The process of claim 8, wherein said acid acceptor is selected from inorganic bases consisting of sodium hydrogen carbonate and potassium carbonate and organic bases consisting of triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo-undec-7-ene, and 1,4-diazabicyclo-octane.

12. The process of claim 8, wherein the reaction is carried out at a temperature ranging from room temperature to 200° C.

13. An antibacterial composition comprising as an active component the compound defined in claim 1, together with a pharmaceutically acceptable carrier.

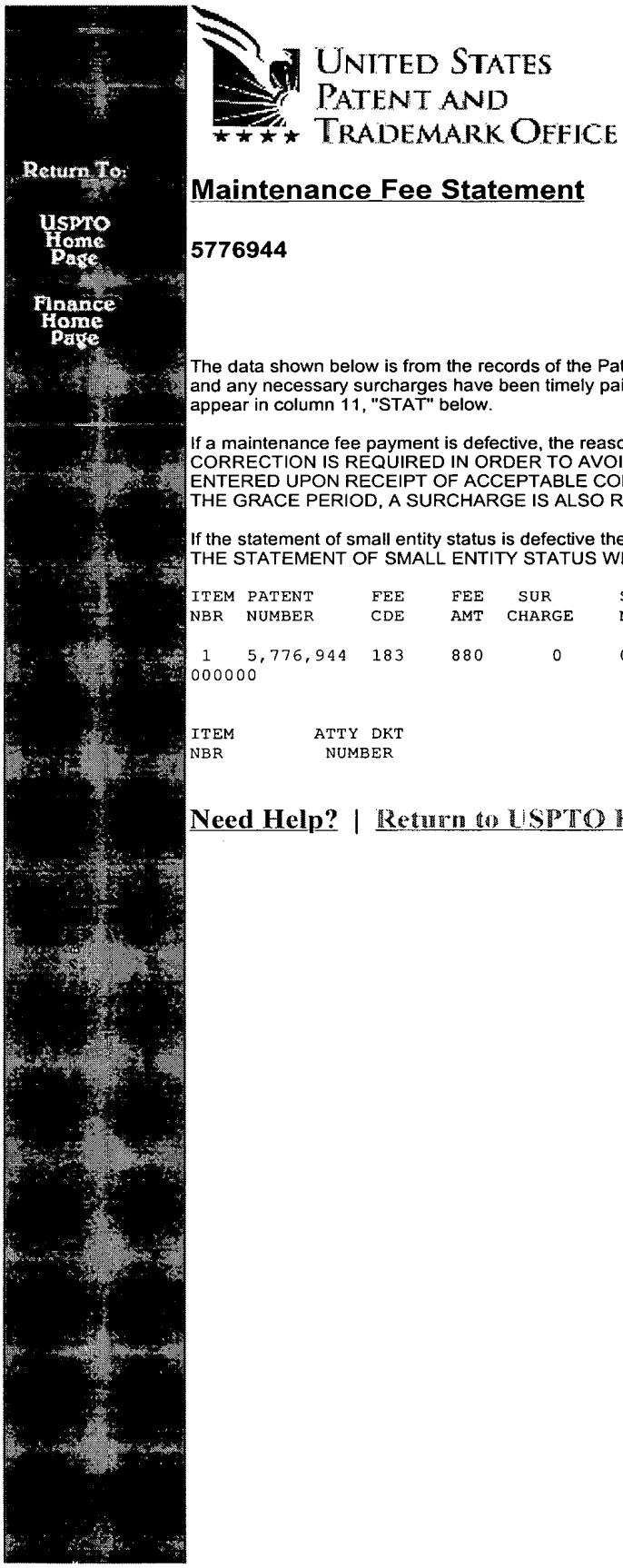
14. The composition of claim 13 comprising 1 to 100 mg of the compound in a unit dosage form.

15. An antibacterial composition comprising as an active component the compound defined in claim 3, together with a pharmaceutically acceptable carrier.

16. The composition of claim 15 comprising 1 to 100 mg of the compound in a unit dosage form.

* * * * *

E



UNITED STATES PATENT AND TRADEMARK OFFICE

Return To:

USPTO Home Page

Finance Home Page

Maintenance Fee Statement

5776944

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,776,944	183	880	0	08/825,992	07/07/98	04/04/97	04	NO	PAID

000000

ITEM NBR	ATTY DKT NUMBER
1	03094.05685

Need Help? | **Return to USPTO Home Page** | **Return to Office of Finance Home P**

F

BRIEF DESCRIPTION OF ACTIVITIES
DURING REGULATORY REVIEW PERIOD FOR FACTIVE®

IND Chronology

August 6, 1997	IND 53,908 filed with FDA.
August 13, 1997	FDA acknowledgement of receipt of IND, assignment of IND number.
August 29, 1997	Comments from FDA as review team completes 30-day review period. Request for teleconference.
August 29, 1997	FDA fax with microbiologist's comments on Etest
September 3, 1997	FDA notification "study is safe to proceed".
September 4, 1997	Serial No. 001: Submit Information Amendment: CMC data to support the physical/chemical characterization of the drug substance. Also submitted one month stability data for drug product.
September 25, 1997	FDA response to questions in the IND cover letter and additional comments regarding IND.
September 26, 1997	Serial No. 002: Submit new protocols: modifications to synopses submitted in IND for Studies 001, 002 and 003.
October 1, 1997	Fax to FDA: overview of Phase I studies data to date
October 20, 1997	Serial No. 003: Submit Protocol Amendment: Change in Protocol (Study 004); Response to FDA Request for Information (reply to Aug 29 fax).
November 14, 1997	Serial No. 004: Submit Information Amendment: Clinical: response to request to include women in Phase I studies Pharm/Tox: submit two 13-week study reports (1-rat/1-dog)

December 4, 1997	Serial No. 005: Submit CMC Information Amendment: change in formulation of SB-265805-S capsules, ofloxacin tablets, and placebos for both study medications.
December 22, 1997	Serial No. 006: Submit Protocol Amendment for new investigators for studies 001, 002, 003 and change in protocol for study 004.
January 20, 1998	Serial No. 007: Protocol amendment for new investigators for studies 001, 002 and 003. Submit final complete report of Phase I pharmacology study (No. 1405/32).
February 17, 1998	New USAN (US Adopted Name) Application
February 27, 1998	Serial No. 008: Submit final reports for four microbiology studies, five assay development studies, one MTD study in dogs and two clinical reports for Phase I protocols.
March 6, 1998	Serial No. 009: Protocol amendment regarding addition of sub-investigators and changes to protocol 003.
March 16, 1998	Discussion with FDA project manager regarding End of Phase II meeting briefing document.
March 31, 1998	Serial No. 010: Submit change in protocol for Study 002, addition of investigator and sub-investigators for Study 003.
April 24, 1998	Serial No. 011: Submit change in protocol for studies 001, 002, 003 and addition of sub-investigators.
May 22, 1998	Discussion with Peter Dionne regarding urine and serology tests rather than cultures to obtain results from "atypical" organisms.
June 16, 1998	Serial No. 012: Request for end of Phase II meeting.

June 18, 1998	Serial No. 013: final study reports for two microbiology studies, one toxicology study and one clinical pharmacology study.
June 29, 1998	Discussion with FDA to schedule end of Phase II meeting and contents of briefing document.
July 7, 1998	Serial No. 014: submit 7 protocols across three indications: CAP (049, 012), ABS (009, 010) and cUTI (013, 014) and study synopses for studies 001 and 003.
July 8, 1998	Discussion with FDA regarding comparators chosen for CAP and uUTI studies. Safety, drug interaction, impairment of effect and labeling also discussed.
July 9, 1998	Fax to FDA containing Note to Reviewer mistakenly omitted from Serial No. 014.
July 13, 1998	Serial No. 015: submit 4 protocols for AECB (008, 068, 069, 070) and study synopsis for Study 002.
July 16, 1998	Serial No. 016: submit Briefing Document for end of Phase II meeting.
July 20, 1998	Discussion with Dr. Alivisatos regarding reporting of SAEs for Phase III trials.
July 27, 1998	Discussion with FDA regarding exporting of drug.
August 3, 1998	Serial No. 017: submit two final toxicology study reports.
August 3, 1998	Fax to FDA regarding revised definition of SAEs, amendment to protocol 014, revised synopsis for protocol 001 and definition of clinical success/failure.
August 4, 1998	Discussion with Dr. Alivisatos regarding protocols to be discussed during end of Phase II meeting.
August 6, 1998	Fax to FDA: microbiological methods for Dr. Alivisatos.

August 11, 1998	End of Phase II Meeting.
August 18, 1998	Fax to FDA regarding Iksan facility and use of 1 month stability data for drug substance.
August 21, 1998	Serial No. 018: CMC Amendment with fully updated drug substance section for the sesquihydrate form to be used in the Phase III trials. Information submitted for the tablet formulation and the various over-encapsulated comparators and matching placebos.
August 25, 1998	Serial No. 019: submit change in protocol for studies 012, 014 and 049.
September 4,1998	FDA Minutes for End of Phase II meeting (August 11, 1998)
September 11, 1998	Serial No. 020 Submit meeting minutes, overheads for the August 11 end of Phase II meeting and CMC sub-meeting.
September 15, 1998	Serial No. 021: Submit protocol amendment for Study 014 (new investigators), Dear Doctor letter regarding rashes and revised patient information and ICF.
September 17, 1998	Serial No. 022: Submit final clinical reports for studies 020 and 034, addendum to final report for Study 006.
September 17, 1998	Discussion with Dr. Schmuff (FDA Chemistry team leader) regarding inclusion of LG (Iksan) facility in the NDA with data from one drug substance batch with 1 month stability data versus the typical 3 months because the plant is currently under construction.
September 22, 1998	Serial No. 023: submit new investigators for Study 014.
September 23, 1998	Serial No. 024: submit SB's position piece on Laboratory Methods for Determination of Infection due to Atypical Pathogens for FDA's consideration, and product labeling for the diagnostic test kits that will be used.

September 28, 1998	Serial No. 025: submit change in protocols and new investigators for Studies 009 and 068.
September 29, 1998	Serial No. 026: submit new investigators for protocol 014.
October 6, 1998	Minutes of July 8, 1998 teleconference faxed by FDA.
October 7, 1998	Serial No. 027: submit new investigators for protocols 009 and 014.
October 12, 1998	Serial No. 028: submit protocol amendment for protocol 008.
October 20, 1998	Serial No. 029: submit new investigators for protocols 008, 009, 012, 014 and 049.
October 22, 1998	Fax to FDA: follow-up to End of Phase II meeting regarding work-up for adolescent patients with joint complaints, and lowering age limit to 16 on protocols 009 and 053.
October 27, 1998	Serial No. 030: submit new investigators for protocol 014.
October 28, 1998	Fax from FDA regarding proposed work-up for adolescent patients with joint complaints. Age limit of 16 years old OK; can proceed with study 009 and complete proposal for study 053.
October 29, 1998	Conversation with FDA regarding clinical plan to work-up joint complaints in adolescents, diagnostic tools for atypical pathogens, obtaining MART reports for trovafloxacin from FOI, and DDMAC issue of the "dual comparator" control regimen for the CAP study.
October 29, 1998	Fax to FDA regarding "dual comparator" control arm (protocol 012) and Zithromax® label.
October 29, 1998	Fax from FDA regarding additional comments from Biopharmaceutics reviewer referencing the End of Phase II Meeting.

October 30, 1998	Recommendation from FDA from pharmacologist to clarify data in report for study SB-265805/RSD-100NT5/1.
November 2, 1998	Serial No. 031: submit new European investigators for protocols 012 and 049.
November 4, 1998	Serial No. 032: submit new investigators for protocols 008, 014 and 068.
November 5, 1998	Serial No, 033: submit new investigators for protocols 009, 012 and 049.
November 6, 1998	Serial No. 034: submit Annual Report.
November 12, 1998	Serial No. 035: submit new investigators for protocols 008, 014 and 068
November 11, 1998	Serial No. 036: submit DMPK report (SB-265805?RSD-100TVN/1).
November 13, 1998	Serial No. 036: submit new European investigators for protocol 012.
November 16, 1998	Serial No. 038: submit new investigators for protocols 009, 012 and 049.
November 16, 1998	Fax to FDA: request to export drug
November 17, 1998	Serial No. 039: submit new investigators for protocols 008, 014 and 068.
November 17 & 18, 1998	Conversations with FDA regarding FOI requests for Trovan™ information.
November 18, 1998	Serial No. 040: submit new protocol 053: 320 or 640mg gemi once per day for 3 days versus 250mg cipro twice daily for 3 days for uUTI.
November 19, 1998	Fax from FDA requesting clarification of Nov 16 fax.

November 19, 1998	Serial No. 041: submit new investigators for protocols 008, 014 and 068.
November 20, 1998	Fax to FDA clarifying Nov16 fax—studies for which drug needs to be exported will not be under US IND.
November 23, 1998	Serial No. 042: submit protocol amendment for study 009 and submission of new protocol, 139.
November 24, 1998	Sent copy of previously submitted protocol 070 (Serial No. 015) for drug export request.
November 25, 1998	Response from USAN Council, acceptance of gemifloxacin mesylate as USAN.
December 3, 1998	Serial No. 043: submit change in protocol 014
December 8, 1998	Serial No. 044: submit new investigators for protocols 008, 014 and 068.
December 11, 1998	Serial No. 045: submit change in protocol 012 and new European investigators for protocols 012 and 049.
December 14, 1998	Serial No. 046: submit new investigators for protocols 008, 014 and 068.
December 16, 1998	Fax from FDA regarding recommendations for protocol 053.
December 17, 1998	Serial No. 047: submit new investigators for protocols 009, 012 and 049.
December 21, 1998	Serial No. 048: submit new investigators for protocols 008, 014 and 068.
December 23, 1998	Submit IND Safety Report (initial).
January 8, 1999	Serial No. 050: submit new investigators for protocols 008, 014 and 053.
January 11, 1999	Serial No. 051: submit new investigators for protocols 009, 012 and 049.

January 14, 1999	Authorization given by FDA to export drug to Estonia.
January 15, 1999	Serial No. 052: submit proprietary name FACTIVE™ and amendment to protocol 068.
January 19, 1999	Serial No. 053: submit new investigators for protocols 008 and 014.
January 20, 1999	Serial No. 054: submit new investigators for protocols 009, 049 and 068.
January 20, 1999	Serial No. 055: submit safety report (follow-up).
January 21, 1999	Serial No. 056: submit new investigators for protocols 008, 014 and 053.
January 29, 1999	Serial No. 057: submit DMPK, microbiology (*in vivo* and *in vitro*) and toxicology reports.
February 2, 1999	Serial No. 058: submit change in protocol and new investigators for protocol 008.
February 3, 1999	Serial No. 059: submit new investigators for protocols 009, 049, 053 and 068.
February 8, 1999	Serial No. 060: submit new protocol 079.
February 10, 1999	FDA Contact Report: discussion about IND for IV formulation.
February 12, 1999	Serial No. 061: submit new investigators for protocols 008, 053 and 068.
February 12, 1999	Fax from FDA with comments from the microbiologist regarding Serial No. 024 affecting the CAP protocols (012 and 049).
February 15, 1999	Serial No. 062: submit new investigators for protocols 014, 053 and 068.
February 16, 1999	Serial No. 063: submit new investigators for protocols 009, 012, 049 and 068.
February 17, 1999	SB fax to FDA listing reasons why cannot agree with microbiologists statements of February 12.

February 18, 1999	Discussion with FDA, reversing microbiologist's position taken on February 12, 1999.
February 19, 1999	Serial No. 064: submit safety report (initial).
February 22, 1999	Serial No. 065: submit change in protocol 049.
February 24, 1999	Serial No. 066: submit new investigators for protocols 008, 053 and 068.
February 26, 1999	Serial No. 067: submit new investigators for protocols 008, 009, 012, 049, 053 and 068.
February 26, 1999	Serial No. 068: submit safety report (initial).
March 8, 1999	Serial No, 069: submit safety report (follow-up).
March 9, 1999	Copy of most recent IB sent to Dr. Powers.
March 9, 1999	Fax from FDA requesting comments on possible effects of gender on the PK of gemifloxacin.
March 11, 1999	Serial No. 070: submit new investigators for protocols 008, 009, 012, 049, 053 and 068.
March 12, 1999	Correspondence from FDA containing questions and comments regarding protocol 049.
March 16, 1999	Serial No. 071: submit new investigators for protocols 012, 104, 049 and 068.
March 16, 1999	Serial No. 072: submit safety report (initial).
March 18, 1999	Serial No. 073: submit updated Investigator Brochure.
March 22, 1999	Serial No. 074: submit response to FDA request for information regarding protocol 079.
March 24, 1999	Serial No. 075: submit new protocol 080.

March 26, 1999	Serial No. 076: submit microbiology, DMPK and toxicology reports.
March 30, 1999	Serial No. 077: submit new investigators for protocols 008, 009, 014, 049 and 053.
March 31, 1999	Serial No. 078: submit new investigators for protocols 008, 009, 012, 014, 049, 053 and 068.
March 31, 1999	Serial No. 079: submit safety report (initial).
March 31, 1999	Serial No. 080: request for pre-NDA meeting.
April 6, 1999	Serial No. 081: submit new investigators for protocols 009, 012, 014, 049 and 053.
April 6, 1999	Fax from FDA regarding nomenclature, Factive accepted with concern.
April 7, 1999	Fax from FDA: OK to proceed with protocol 080.
April 7, 1999	Serial No. 082: response to FDA request for information regarding protocol 053.
April 8, 1999	FDA schedules pre-NDA meeting for May 27, 1999
April 11, 1999	Fax from FDA regarding issues for QT teleconference.
April 13, 1999	Serial No. 083: submit change in protocol 012.
April 15, 1999	Serial No. 084: submit new investigators for protocols 012, 014, 049 and 053.
April 16, 1999	Serial No. 085: submit new investigators for protocols 008, 012, 014, 049, 053 and 068.
April 16, 1999	Serial No. 086: submit safety report (follow-up).
April 20, 1999	Serial No. 087: submit DMPK report.
April 23, 1999	Serial No. 088: submit safety report (initial).

April 26, 1999	Serial No. 089: submit new investigators for protocols 012, 014, 049 and 053.
April 28, 1999	Serial No. 090: submit DMPK and chemistry report.
April 29, 1999	Serial No. 091: submit response to FDA request for information contains revised criteria for serologic diagnosis of *C. pneumoniae* infection.
April 29, 1999	Serial No. 092: submit pre-NDA briefing document.
May 7, 1999	Serial No. 093: submit new investigators for protocols 014, 053 and 068.
May 7, 1999	Serial No. 094: submit new investigators for protocols 008, 012, 014 and 049.
May 7, 1999	Serial No. 095: submit final clinical study report for protocol 003.
May 7, 1999	Serial No. 096: submit new protocol and investigator for Study 126.
May 12, 1999	Serial No. 097: request for pre-IND/pre-Phase III meeting (for IV formulation).
May 12, 1999	Correspondence from FDA authorizing export of investigational drug to Mexico.
May 12, 1999	Fax from FDA regarding diagnosis of atypical organisms.
May 12, 1999	Serial No. 098: submit DMPK reports.
May 18, 1999	Serial No. 099: submit safety report (initial).
May 20, 1999	Serial No. 100: submit change in protocol 014.
May 20, 1999	SB fax to FDA regarding electronic submission plans for NDA.
May 20, 1999	FDA fax comments regarding questions in pre-NDA briefing document.

May 21, 1999	Serial No. 101: submit new investigators for protocols 008, 049 and 068.
May 25, 1999	SB faxed responses to comments received from FDA on May 20, 1999.
May 26, 1999	Serial No. 102: submit DMPK and toxicology reports.
May 27, 1999	Pre-NDA Meeting.
June 1, 1999	Fax from FDA: OK to proceed with protocol 126.
June 3, 1999	Serial No. 103: submit new investigators for protocols 008, 014, 053 and 126.
June 10, 1999	Fax from FDA scheduling meeting for IV formulation on July 13, 1999.
June 11, 1999	Serial No. 104: submit end of Phase II briefing document for IV meeting.
June 14, 1999	Serial No. 105: submit new investigators for protocols 008, 009, 049, 053 and 126.
June 15, 1999	Serial No. 106: submit change in protocol 068.
June 15, 1999	SB fax to FDA regarding IND for IV formulation.
June 22, 1999	Serial No. 107: DMPK and microbiology reports.
June 22, 1999	Fax from FDA regarding filing of separate IND for IV formulation and clinical reports to be submitted in NDA.
June 28, 1999	Serial No. 108: Submit preclinicial safety report (initial) regarding results of rat pre- and postnatal reproductive toxicology.
June 30, 1999	Serial No. 109: submit new investigators for protocols 049, 068 and126.
June 30, 1999	Serial No. 110: submit new investigators for protocols 008, 012, 014, 049, 053, 068 and 126.

June 30, 1999	Fax from FDA with comments from microbiologist regarding Serial No. 057.
July 1, 1999	Serial No. 111: submit microbiology reports.
July 2, 1999	FDA teleconference regarding the clastogenic findings from *in vivo* intravenous rat micronucleus study.
July 2, 1999	Serial No. 112: submit final clinical study reports for protocols 019, 021, 022, 023 and 084.
July 6, 1999	FDA contact report trying to schedule telecon with Dr. Ellis to discuss rat clastogenicity (Serial No. 113).
July 8, 1999	FDA contact report postponing July 13 IV meeting and requested telecon with Dr. Ellis.
July 14, 1999	Discussion with Peter Dionne regarding microbiology reports submitted july 1 (Serial No. 111).
July 16, 1999	Serial No. 113: submit preclinical safety report for rat micronucleus test results.
July 16, 1999	FDA contact report postponing IV meeting and results of *in vivo* rat micronucleus test.
July 22, 1999	Serial No. 114: submit new investigators for protocols 014 and 049.
July 26, 1999	Fax from FDA granting official acceptance of FACTIVE™ name.
July 27, 1999	Serial No. 115: submit meeting minutes for pre-NDA meeting held on May 27.
July 28, 1999	Serial No. 116: response to FDA questions raised by Peter Dionne.
August 5, 1999	Serial No. 117: submit new investigators for protocols 009, 068 and 126.
August 12, 1999	Serial No. 118: submit new investigators for protocols 008, 009, 012, 014, 049, 053 and 068.
August 16, 1999	SB faxed summary of protocol 082 results to Division.
August 16, 1999	Serial No 119: submit new investigators for protocols 008, 012, 014, 049, 053, 068 and 126.

August 16, 1999	FDA response to questions in the briefing document for IV formulation meeting scheduled for August 31, 1999.
August 18, 1999	Serial No. 120: submit end of Phase II briefing document update for IV formulation.
August 19, 1999	Serial No. 121: submit safety report (follow-up).
August 23, 1999	Serial No. 122: submit new investigators for protocols 009, 012, 068 and 126.
August 25, 1999	Fax from FDA with May 27/pre-NDA meeting minutes.
August 31, 1999	Pre-IND meeting for IV formulation.
September 2, 1999	Questions faxed to Division regarding contents and structure of NDA.
September 10, 1999	FDA response to Sept 2 fax.
September 14, 1999	Serial No. 123: submit changes to investigator information previously submitted for protocols 008, 009, 012, 014, 049, 053 and 068.
September 24, 1999	Serial No. 124: submit amendment to CMC data.
September 23, 1999	Serial No. 125: submit new investigators and changes to current investigator information for protocol 126.
September 27, 1999	Serial No. 126: submit results of further investigations of the *in vivo* clastogenic potential of gemi.
September 29, 1999	Serial No. 127: submit update for items discussed during the EoPII meeting in August 1998. Items include: starting materials for drug substance, process improvement, additional sites for manufacture of drug substance, biostudies and dissolution and other misc. items.
October 6, 1999	Serial No. 128: request for FDA opinion regarding design of protocol 111 for IV formulation.

October 6, 1999	Serial No. 129: submit safety report (initial).
October 12, 1999	SB faxed confirmation of October 14 telecon to ascertain which type of data display FDA would find most appropriate for the presentation of plasma concentration results. Two examples faxed.
October 14, 1999	Teleconference with FDA regarding plasma concentration data display.
October 15, 1999	Serial No. 130: submit investigator revisions for protocols 068 and 126.
October 18, 1999	Serial No. 131: submit termination of study 126.
October 22, 1999	Teleconference with FDA regarding Study 111.
November 2, 1999	FDA faxed minutes of October 22 teleconference.
November 5, 1999	Serial No. 132: submit Annual Report
November 11, 1999	Serial No. 133: submit new protocol 105.
November 15, 1999	Submit Gemifloxacin Mesylate DMF 14524.
November 17, 1999	Serial No. 134: submit new protocol 206.
November 18, 1999	Serial No. 135: submit new protocol 186.
November 23, 1999	Serial No. 136: submit new protocol 207.
November 30, 1999	FDA Contact Report: Dr. Powers requested copy of a CFR for protocol 105.
December 1, 1999	Fax to FDA with intent of study 105.
December 2, 1999	Fax from FDA with questions about recently submitted protocols.

December 2, 1999	Fax from FDA: OK to proceed with protocol 105.
December 2, 1999	Serial No. 138: submit response to request for further information for protocol 105.
December 6, 1999	SB faxed to FDA intent and start dates of protocols 185, 186, 206 and 207.
December 6, 1999	Fax from FDA: OK to proceed with protocol 185.
December 16, 1999	Serial No. 139: submit new protocol 112 and request for FDA opinion of protocol.
December 29, 1999	Serial No. 140: submit response to FDA request for information regarding protocol 105.
January 4, 2000	Serial No. 141: submit new investigators for protocols 112, 185 and 206.
January 7, 2000	Serial No. 142: Submit request for FDA opinion on revised protocol 111 (IV study).
January 14, 2000	Serial No. 143: response to FDA comments on protocols 105, 186, 206 and 207.
January 14, 2000	Serial No. 144: submit new investigators for protocols 105 and 185.
January 14, 2000	Serial No. 145: submit new investigators for protocols 186 and 206.
January 17, 2000	Serial No.146: submit new investigators for protocol 207.
January 18, 2000	Serial No. 147: submit amendment to protocol 185.
January 26, 2000	Serial No. 148: response to FDA comments on protocol 185.
January 21, 2000	Serial No. 149: response to FDA comments on protocol 112.
February 3, 2000	Serial No. 150: submit new investigators for protocols 112, 185 and 206.
February 4, 2000	Serial No. 151: submit new investigators for protocol 112.

February 7, 2000	E-mail request from FDA for American Thoracic Society (ATS) statement on obtaining measurements of FEV1.
February 14, 2000	SB sends publication with ATS statement to FDA electronically.
February 16, 2000	Serial No. 152: submit new investigators and revised investigator information for protocols 008, 009, 012, 014, 049, 053, 068 and 126.
February 16, 2000	Serial No. 153: official submission of ATS statement.
February 25, 2000	Serial No. 154: submit new investigators for protocols 105, 206 and 207.
February 28, 2000	Serial No. 155: submit new investigators for protocol 185.
February 28, 2000	Serial No. 156: submit response to FDA faxed comments for protocol 111.
February 28, 2000	Serial No. 157: submit response to FDA comments on protocol 105.
February 29, 2000	Serial No. 158: submit new investigators for protocol 112.
March 1, 2000	Fax from FDA: comments on protocol 111.
March 2, 2000	Serial No. 159: submit new investigators for protocols 105, 112, 185 and 206.
March 2, 2000	Serial No. 160: submit new investigators for protocols 112 and 186.
March 6, 2000	Serial No. 161: submit investigator information revisions for protocols 008, 009, 012, 014, 049 and 068.
March 7, 2000	Serial No. 162: submit response to FDA comments on protocol 112.
March 14, 2000	Serial No. 163: submit new investigators and investigator revisions for protocols 112, 185, 186 and 207.
March 16, 2000	Serial No. 164: submit new investigators for protocols 105, 112, 185 and 206.

March 28, 2000	Serial No. 165: submit new investigators and investigator revisions for protocols 105, 112, 185, 186 and 207.
April 13, 2000	Serial No. 166: submit safety report (initial).
April 14, 2000	Serial No. 167: submit amendment for protocol 112.
April 18, 2000	Serial No. 168: submit new investigators and investigator revisions for protocols 105, 112, 185 and 207.
April 19, 2000	Serial No. 169: submit new investigators and investigator revisions for protocols 009, 014, 049 and 126.
April 19, 2000	Serial No. 170: submit amendment for protocol 139.
April 26, 2000	Serial No. 171: submit amendment for protocol 206.
Apirl 26, 2000	Serial No. 172: submit new investigators and investigator revisions for protocols 105, 112 and 206.
April 27, 2000	Serial No. 173: submit new investigators and investigator revisions for protocols 112, 185, 186 and 207.
May 9, 2000	FDA fax on evaluation of Acute Sinusitis Patients.
May 11, 2000	Serial No. 174: submit revised IB (5^{th} edition).
May 22, 2000	Serial No. 175: submit response to FDA questions regarding protocol 112 and request for a meeting with FDA to discuss protocols 112 and 139.
May 24, 2000	Serial No. 176: submit new investigators and investigator revisions for protocols 105, 112, 185, 186 and 207.
May 31, 2000	Serial No. 177: submit new investigator and investigator revisions for protocols 112, 185 and 206.

June 5, 2000	FDA fax scheduling meeting to discuss protocols 112 and 139 on June 28, 2000 (Type C meeting).
June 9, 2000	Serial No. 178: submit new investigators and investigator revisions for protocol 112.
June 13, 2000	Serial No. 179: request to postpone June 28 meeting.
June 27, 2000	Serial No. 180: submit safety report (follow-up).
June 30, 2000	Serial No. 181: submit new investigators and investigator revisions for protocols 112, 185 and 206.
July 6, 2000	Serial No. 182: submit amendment for protocol 080.
July 7, 2000	Serial No. 183: submit CMC amendment to extend shelf life from 24 to 36 months.
July 13, 2000	Serial No. 184: submit new investigators and investigator revisions for protocols 112 and 185.
July 18, 2000	Submit a revised version of the report for Study 037 (Serial No. 185) entitled "An open, randomized, two-way crossover study to assess the penetration of gemifloxacin at steady-state into bronchial mucosa and bronchoalveolar lavage fluid in healthy volunteers".
July 31, 2000	Serial No. 186: submit new protocol 212.
August 1, 2000	Serial No. 187: submit safety report (initial).
August 3, 2000	Serial No. 188: submit request for FDA meeting (rescheduling of meeting to discuss protocols 112 and 139.)
August 10, 2000	Serial No. 189: submit new investigators and investigator revisions for protocols 112 and 206.
August 11, 2000	Serial No. 190: submit amendment and modification of protocol 105.
August 23, 2000	Serial No. 191: submit safety report (follow-up).

August 24, 2000	Fax from FDA: OK to proceed with protocol 212.
August 25, 2000	Serial No. 192: submit new investigators and investigator revisions for protocol 112.
August 31, 2000	Serial No. 194: submit new protocol 287.
September 8, 2000	FDA Correspondence: schedule Type C meeting to discuss protocols 112 and 139 on November 7, 2000.
September 13, 2000	Serial No. 195: submit new investigators and investigator revisions for protocols 112 and 212.
September 15, 2000	Serial No. 196: submit new investigators and investigator revisions for protocols 112 and 287.
September 15, 2000	Serial No. 197: submit response to FDA comments on protocol 212.
September 29, 2000	Serial No. 198: submit new investigators and investigator revisions for protocols 112, 185, 212 and 287.
October 8, 2000	Fax from FDA regarding concerns with protocols 287 and 107.
October 9, 2000	Serial No. 199: submit end of Phase II (EoPII) briefing document.
October 12, 2000	Serial No. 200: submit new investigators and investigator revisions for protocols 112, 212 and 287.
October 18, 2000	Serial No. 201: submit new investigators and investigator revisions for protocols 212 and 287.
October 27, 2000	Serial No. 202: submit Annual Report
November 14, 2000	Serial No. 203: submit new investigators and investigator revisions for protocols 112, 206, 212 and 287.
November 22, 2000	Serial No. 204: submit DMPK report

November 30, 2000	Serial No. 205: submit new investigators for protocols 185, 186, 212 and 287.
	Serial No. 206 (N/A)
January 10, 2001	Serial No. 207: submit amendment and new investigators for protocol 287.
January 22, 2001	SB request to export drug to China.
January 26, 2001	Serial No. 208: submit amendment and new investigators for protocol 287.
January 29, 2001	Serial No. 209: submit amendment and investigator revisions for protocol 212.
January 30, 2001	Serial No. 210: submit new protocol 333.
February 26, 2001	Serial No. 211: submit new investigators for protocol 333.
February 26, 2001	Fax from FDA regarding protocol 333, OK to proceed, but have comments.
March 1, 2001	Serial No. 212: response to request for information on patient with possible pustular dermatosis.
March 12, 2001	Serial No. 213: investigator revisions for protocols 112, 212 and 287; new investigators for protocol 333.
April 17, 2001	Serial No. 214: submit DMPK report
April 17, 2001	Serial No. 215: submit new protocol 344.
April 19, 2001	Serial No. 216: submit investigator revisions for protocols 112, 212 and 287; new investigators for protocol 333.
May 7, 2001	SB fax to FDA with safety report (initial)
May 8, 2001	Fax from FDA: OK to proceed with protocol 344, but have comments.

May 11, 2001	Serial No. 217: submit official safety report (initial), faxed on May 7, 2000.
May 22, 2001	Serial No. 218: submit investigator revisions for protocols 112, 287 and 333; new investigators for protocol 344.
June 7, 2001	Serial No. 219: submit final clinical study report for protocol 185.
June 8, 2001	Serial No. 220: submit safety report (initial).
June 11, 2001	Serial No. 221: submit amendment and new investigators for protocol 344.
June 14, 2001	Serial No. 222: submit new investigators and investigator revisions for protocols 287, 333 and 344.
June 22, 2001	Serial No. 223: submit final clinical study report for protocol 077.
June 22, 2001	Serial No. 224: submit final clinical study report for protocol 062.
June 27, 2001	Serial No. 225: submit final clinical study report for protocol 059.
June 27, 2001	Serial No. 226: submit safety report (initial).
July 5, 2001	Serial No. 227: submit final clinical study report for protocol 036.
July 6, 2001	Serial No. 228: submit final clinical study report for protocol 033.
July 13, 2001	Serial No. 229: submit new investigators and investigator revisions for protocols: 112, 212, 287, 333 and 344.
July 20, 2001	Serial No. 230: submit safety report (follow-up)
August 2, 2001	Serial No. 231: submit new investigators and investigator revisions for protocols 287, 333 and 344.
August 9, 2001	Serial No. 232: submit DMPK reports.

August 2001	Serial No. 233: to be clarified w/ GSK.
August 22, 2001	Serial No. 234: submit DMPK reports.
September 10, 2001	Serial No. 235: submit new investigators and investigator revisions for protocols 287, 333 and 344.
September 12, 2001	Serial No. 236: submit new investigators and investigator revisions for protocols 287 and 344.
September 17, 2001	Serial No. 237: submit new investigators for protocol 333.
September 19, 2001	Serial No. 238: submit DMPK report.
September 27, 2001	Serial No. 239: new investigators and investigator revisions for protocol 344.
October 22, 2001	Serial No. 240: submit new investigators and investigator revisions for protocols 287 and 333.
October 25, 2001	Serial No. 241: submit safety report (follow-up).
October 30 ,2001	Serial No. 242: submit new investigators and investigator revisions for protocols 185, 287, 333 and 344.
November 6, 2001	Serial No. 243: submit Annual Report
February 4, 2002	Serial No. 244: submit new investigators for protocols 287 and 333.
February 28, 2002	Serial No. 245: submit new investigators for protocols 287 and 333.
April 4, 2002	Serial No. 246: new investigators and investigator revisions for protocols 287, 333 and 344.
April 22, 2002	Serial No. 247: submit new investigators and investigator revisions for protocols 287 and 333.
June 5, 2002	Serial No. 248: submit new investigators and investigator revisions for protocols 287 and 333.

June 26, 2002	Serial No. 249: submit nonclinical study reports: SB-265805/RSD101MCG/1, SB-265805/RSD-101MGD/1, General/RSD-1018F1/1 and SB-265805/RSD-101BT0/2.
July 11, 2002	Serial No. 250: submit nonclinical study reports: SB-265805/RSD-101GVB/1, SB-265805/RSD-101MG9/1, SB-265805/RSD-101MGB/1, SB-265805/RSD-101N65/2 and SB-265805/RSD-101NB3/1.
July 25, 2002	Serial No. 251: submit response to FDA request for patient profiles and datasets for study 185.
July 29, 2002	Serial No. 252: submit response to FDA request for specific listings for study 185.
August 5, 2002	Serial No. 253: submit abridged clinical study reports for protocols 001, 003, 008, 009, 010, 013, 049, 053, 067 and 068.
August 6, 2002	Serial No. 254: submit 34 microbiology reports.
August 13, 2002	Serial No. 255: submit DMPK and pharmacology reports.
August 16, 2002	Serial no. 256: submit final clinical study reports for protocols 024, 056, 114 and 344.
August 20, 2002	Serial No. 257: submit a microbiology report, SB-265805/RSD-101TRW/1.
August 22, 2002	Serial No. 258: submit response to FDA request for information regarding study 185.
August 23, 2002	Serial No. 259: submit response to FDA request for CRFs for protocol 185.
August 29, 2002	Serial No. 260: submit revised investigator information for protocol 287.
September 13, 2002	Serial No. 261: submit clinical study reports for protocols 105, 112, 139, 207 and 212.

September 17, 2002	Serial No. 262: submit missing Vol 17 of 25 for Serial No. 261.
September 24, 2002	Serial No. 263: submit IND transfer from GSK to LGLS.
September 26, 2002	Serial No. 264: submit acceptance of IND transfer and transfer of obligations to PAREXEL.
October 21, 2002	Serial No. 265: submit response to request for additional CRFs for study 185.
December 19, 2002	Serial No. 266: submit Annual Report.
December 31, 2002	Submit clinical reports for studies 106, 107, 111 under IND No. 60,132.
January 3, 2003	Serial No. 267: submit clinical study reports for protocols 303 and 333.
April 8, 2003	Serial No. 268: submit clinical pharmacology reports for protocols 044, 060, 062, 075, 079, 080, 245, 249 and 250.

NDA Chronology

December 15, 1999	NDA 21-158 submitted to FDA.
December 27, 1999	Acknowledgement from FDA receiving the NDA package for review.
December 28, 1999	Request for statistical plan change clarifications in studies SB-265805/013 and SB-265805/014.
December 30, 1999	Request for listing of duration of therapy in studies SB-265805/013 and SB-265805/014.
January 4, 2000	Response to request for word document files for the reports of studies SB-265805/013 and SB-265805/014.
January 6, 2000	Response to request for clarification/information regarding clinical studies SB-265805/013 and SB-265805/014.
January 10, 2000	Submit Field Copy of NDA 21-158.

January 18, 2000	Response to request for patient profiles (CRTs) for the clinical trials contained in NDA 21-158.
January 21, 2000	Request for 8-month safety update.
February 8, 2000	Fileability of NDA confirmed by FDA.
February 17, 2000	Request for additional regression analyses comparing plasma drug Cmax to change in QTc, and plasma drug concentration to time of maximal change in QTc.
February 18, 2000	Response to request regarding FDA's proposed inspection of the investigators.
February 23, 2000	Request for samples (Drug Product, Drug Substance) to perform methods validation.
March 2, 2000	Response to FDA request for x-ray assessment reports for the patients in studies 009, 010, 011, 012, and 049.
March 7, 2000	Response to "Method Validation Letter" dated February 23, 2000. Submit copies of specification, methods and validations detailed in LG Chemical's DMF 14524 for Gemifloxacin Mesylate.
March 7, 2000	Response to request letter dated February 17, 2000.
March 13, 2000	Pre-announcement of PAI (Pre-Approval Inspection) for primary manufacturing site located at Iksan, Korea.
March 22, 2000	Response to provide accommodation details for PAI of Iksan site.
March 23, 2000	Response to request for ECG data.
March 31, 2000	Response to request for a full waiver for conducting pediatric studies.
April 27, 2000	FDA notice of non-approval for Acute Pyelonephritis indication.
May 1~3, 2000	PAI of Iksan site.

May 19, 2000	Submit "coming soon" campaign for Factive® logo.
May 30, 2000	Response on Factive®'s lack of efficacy data in acute pyelonephritis referenced in the letter dated April 27, 2000.
June 1, 2000	Request for additional information related to CAP studies.
June 15, 20, 27, 2000	Responses to request for information regarding CAP studies.
June 27, 2000	Amendment to Pending NDA 21-158: current and correct analytical method "Determination of Impurities and Degradations for SB-265805-S by HPLC".
July 21, 2000	Amendment to Pending Application: pharmacokinetic data for comparator drug, trovafloxacin, in study 037 and revision of macrophage concentrations of gemifloxacin.
August 8, 2000	Request for additional information regarding NDA submission.
August 10, 2000	Provided comments on the microbiology section of the proposed labeling.
August 14, 2000	Submit 8-month Safety Update.
August 15, 2000	Response to request dated August 8, 2000.
August 15, 2000	Request for supporting data used in March 7th submission on QTc issues.
August 18, 2000	Response to request dated August 15, 2000.
August 24, 2000	Response to request for clarification and/or additional information on some of the data from the CAP, ABS and AECB clinical trials.

September 1, 2000	Submit revised microbiology section of the labeling in accordance with FDA comments dated August 10, 2000.
September 1, 2000	EIR (Establishment Inspection Report) issued for Iksan PAI.
September 8, 2000	Request to export drug to the People's Republic of China to be used as clinical trial supplies.
September 26, 29, 2000	Requests (I) for additional safety information.
September 26, 28, 2000	Response on safety information.
October 2, 10, 2000	Request (II) for additional safety information.
October 9, 2000	Response to request for statistical appendices for the clinical studies.
October 11, 16, 17, 2000	Responses to additional questions on rash.
October 19, 2000	Submit previous agreements with the Division on packaging.
October 25, 2000	Receive FDA labeling counterproposal.
October 31, 2000	Submit Briefing Document for November 7, 2000 Meeting to discuss FDA's concerns.
November 3, 2000	Response to request for additional information on NDA 21-158.
November 7, 2000	Face to Face Meeting to discuss safety concerns (rash, hepatotoxicity, QT prolongation).
November 21, 2000	Response to request for additional information on rash issues.
November 24, 2000	Request for a meeting w/ Director of CDER.
November 27, 2000	Response to request for "benefits" summary.

November 28, 2000	Response to request for letters from consultants who were mentioned in October 31, 2000 meeting package.
December 4, 2000	Request for additional information regarding CMC.
December 7, 2000	Comments provided on FDA Meeting Minutes regarding November 7, 2000 Meeting.
December 8, 2000	Response to CMC deficiency questions.
December 15, 2000	Non-Approvable Letter for NDA 21-158.
December 22, 2000	Notice for a meeting delay regarding action letter
January 12, 2001	Request for a meeting to discuss clinical safety of Factive®
January 19, 2001	FDA confirmation of a type A meeting on February 22, 2001
February 6, 2001	Submit Briefing Document for February 22, 2001 Meeting.
February 22, 2001	Face to Face Meeting on Resubmission Proposal
March 9, 2001	Submit Minutes of the February 22, 2001 Meeting.
March 16, 2001	Request for additional information on rash.
April 4, 2001	Response to request for a reference to support the statistical methodology proposed to be used in the analysis of the 'rash' data to be acquired from clinical studies 265805/344 and 265805/345.
April 10, 2001	Response to request for tabular displays of rash data.
April 12, 2001	Submit 2nd Safety Update DAP (Dossier Analysis Plan).
April 24, 2001	Receipt of User Fee ID Assignment.

April 25 ~ October 17, 2001	Conduct study 344 to address FDA concerns: A two part study to characterize the histology and clinical features of rash associated with gemifloxacin and to assess the potential for cross-sensitization to another quinolone in healthy female volunteers.
June 5, 2001	Response to request for further rash analysis data.
June 14, 2001	Submit NDA 21-376 for 5-day ABS (Acute Bacterial Sinusitis).
July 19, 2001	FDA notice that NDA 21-376 cannot receive an "Approval" action without the additional safety data relating to rash.
August 3, 2001	Request for teleconference regarding submission of additional PRSP (penicillin-resistant *S. pneumoniae*) data.
August 14, 2001	Request for iv program clarifications and CRTs/CRFs for study 344.
August 17, 2001	Request for Interim Study Report for Study 287.
August 21, 2001	Request for 18-month Safety Update without Dr. Passage's Date, study 186 report revisions without Dr. Passage's data.
August 23, 2001	Amendment to NDA 21-376: revised key efficacy and safety tables for study 265805/206.
September 4, 2001	Response to request for clinical documents regarding FDA inspection of the investigators.
October 18, 2001	Amendment to NDA 21-376: revised study 186 key efficacy and safety tables, revised ISS key safety tables.
January 8, 2002	Request for a meeting to discuss approvability of NDA 21-158 and 21-376 based on new data for rash and CAP (community-acquired pneumonia) studies.

January 18, 2002	Acknowledgement of February 27, 2002 Face to Face Meeting.
February 12, 2002	Submit Briefing Document for February 27, 2002 Meeting.
February 22, 2002	Submit DMF Annual Update.
February 27, 2002	Type A Face to Face Meeting regarding NDA Resubmission.
April 9, 2002	GlaxoSmithKline (GSK) termination letter to LG Life Sciences.
April 12, 2002	Non-Approvable Letter for NDA 21-376.
April 18, 2002	Notification of Intent to Amend Application NDA 21-376.
May 31, 2002	LG/Parexel Agreement for Services signed. Parexel to act as U.S. agent.
July 2, 2002	Teleconference (FDA/GSK/LG Life Sciences/Parexel) to discuss Factive® transfer and resubmission.
August 23, 2002	LG/GeneSoft Pharmaceuticals Memorandum of Understanding signed. GeneSoft Pharmaceuticals to be U.S. commercial partner.
September 11, 2002	Request for additional information on study 185 and CRFs for patients with *Legionella pneumophila*.
September 26, 2002	Transfer of IND/NDA sponsorship from GlaxoSmithKline to LG Life Sciences, Parexel as U.S. Agent.
October 4, 2002	Resubmission to NDA 21-158 filed.
October 14, 2002	Submit AECB efficacy data: individual study reports for the new studies 105, 112, 139, 207, 212 and 298.
October 14, 2002	LG/GSK Termination Agreement signed.

October 21, 2002	Reponse to request dated September 11, 2002.
October 22, 2002	LG/GeneSoft License and Option Agreement signed.
October 23, 2002	Request for select study 287 Case Report Tabulations missing from October 4, 2002 resubmission.
October 31, 2002	Teleconference to discuss updating of safety information.
November 6, 2002	Request for additional data and analyses that pertain to studies 303, 333 and 287 as well as the CAP-IV studies 106, 107, 111.
November 8, 2002	Request for table containing Class 4/5 patients in all studies in the resubmission except study 185.
November 25, 2002	Acknowledgement of October 4, 2002 resubmission as a complete, class 2 response to December 15, 2000 action letter.
November 25, 2002	Teleconference to discuss submission timeline of study reports, possibility of further safety update and face to face meeting.
November 27, 2002	Request for information regarding inspection of a site that participated in study 344.
December 2, 2002	Receive FDA letter outlined procedures for the Anti-Infective Drugs Advisory Committee Meeting scheduled for March 4, 2003.
December 6, 2002	Request for follow-up information for two sudden cardiac deaths in studies 106 and 112.
December 9, 2002	Response to request for patient listings, rash data and investigator information for protocol SB 265805/344 stated in the November 27 letter.
December 12, 2002	Request for investigator list and Vol 1.1 of the Resubmission.
December 16, 2002	Request for pregnancy outcomes for patients in study 344.

December 20, 2002	Response to requests dated December 9, 2002 and December 16, 2002.
December 23, 2003	Request for additional information regarding safety update.
December 30, 2002	Submit Briefing Package for January 22, 2003 Teleconference.
December 30, 2002	Submit CMC amendment.
December 31, 2002	Request for additional information regarding PRSP and CAP data.
January 6, 2003	Division meeting to discuss Factive® Resubmission.
January 7, 2003	Request for additional information regarding extent of exposure table for all *S. pneumoniae* patients.
January 13, 2003	Request for additional information from Biopharmaceutics and Clinical Pharmacology reviewers.
January 15, 2003	Federal Register notice of March 4, 2003 meeting of the Anti-Infective Drugs Advisory Committee.
January 16, 2003	Response to request dated December 31, 2002.
January 22, 2003	Request for a table summarizing rates of rash in all AECB studies by sex, age and duration of treatment received.
January 22, 2003	Teleconference to discuss briefing document for March 4 Advisory Committee Meeting.
January 24, 2003	Response to request dated January 13, 2003.
January 27, 2003	Request for additional hepatotoxicity data.
January 27, 2003	Request for changes to Advisory Committee Background Package.

January 30, 2003	Submit Background Package for Advisory Committee Meeting.
February 3, 2003	Request for additional information regarding patients who received macrolides in the CAP studies.
February 4, 2003	Request for a table listing number of patients with *S. pneumoniae* and PRSP.
February 11, 2003	Response to requests dated January 7, 2003, February 3, 2003, February 4, 2003, January 22, 2003, and January 27, 2003.
February 13, 2003	Receive FDA Background Package and Advisory Committee List.
February 25, 2003	Face to Face Meeting to discuss about FDA Advisory Committee Meeting preparation.
March 4, 2003	FDA Anti-Infective Drugs Advisory Committee Meeting on Factive®.
March 7, 2003	Request for analysis of occurrence of rash by age and gender of subjects.
March 7, 2003	Teleconference to discuss next steps after Advisory Committee Meeting.
March 12, 2003	Submit revised labeling and foil packs.
March 17, 2003	Request for a listing of subjects diagnosed with *S. pneumoniae* demonstrating tetracycline and TMP-SMX resistance.
March 21, 2003	Teleconference to discuss tetracycline/TMP-SMX use affecting rash.
March 25, 2003	Teleconference regarding labels for cartons and blister foils.
March 26, 2003	Receive comments from Pharmacology/Toxicology reviewer.
March 27, 2003	Response to requests dated March 7, 2003 and March 17, 2003.

March 27, 2003	Teleconference regarding post-marketing pharmacovigilance plan.
March 28, 2003	Submit written confirmation of the agreements reached during March 27, 2003 teleconference.
March 28, 2003	Submit revised labels for cartons and blister foils agreed during March 25, 2003 teleconference.
March 31, 2003	Teleconference to discuss options for submitting additional information for the multi-drug resistant *S. pneumoniae* (MDRSP) claim.
April 1, 2003	Submit Patent Information.
April 2, 2003	Teleconference regarding carton labels and labeling discussions.
April 3, 2003	Submit revised packaging and the final draft labeling.
April 4, 2003	Approval Letter: Factive® granted approval for commercial marketing in U.S.

G

PATENT
Atty. Docket No.: 9009.0008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,776,944)
)
Issued: July 7, 1998)
)
To: Chang Y. Hong, Young K. Kim, Se H. Kim,)
Jay H. Chang, Hoon Choi, Do H. Nam,)
Ae R. Kim, Jin H. Lee, Ki S. Park)
)
Assignee: LG Life Sciences, Ltd.)

For: 7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROPLIDIN-1-YL)-1-CYCLOPROPYL-6-FLUORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF

MAIL STOP: PATENT EXT.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

CERTIFICATION

I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 5,776,944 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: May 29, 2003

By: Charles E Van Horn
Charles E. Van Horn
Reg. No. 40,266

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In Re U.S. Patent No. 5,776,944

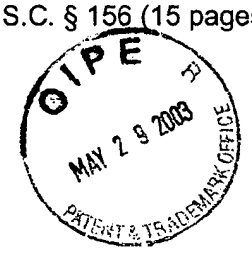
Issued: July 7, 1998

To: Chang Y. Hong, Young K. Kim, Se. H. Kim, Jay H. Chang, Hoon Choi, Do H. Nam, Ae R. Kim, Jin H. Lee, Ki S. Park

Assignee: LG Life Sciences, Ltd.

For: 7-(4-AMINOMETHYL-3-METHYLOXYIMINOPYRROLIDIN-1-YL)-1-CYCLOPROPYL-6-FLUORO-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID AND THE PROCESS FOR THE PREPARATION THEREOF

1. Application for Extension of Patent Term Under 35 U.S.C. § 156 (15 pages - Original & 4 copies with Attachments A-G
   - A. Power of Attorney
   - B. Approval Letter
   - C. Approved Labeling Information for FACTIVE®
   - D. U.S. Patent 5,776,944
   - E. Maintenance Fees Paid
   - F. Chronology of Regulatory Review Period
   - G. Certification of Copies of Application Papers



2. Check in the amount of $1,120.00 in payment of PTE fee

Dated May 29, 2003

Docket No.: 09009.0008 (due date 6/3/03)

C.E. Van Horn/C. Woods - Mail Drop 318 **ATTN: ELIZABETH POLLEY**

HAND CARRY TO OFFICE OF PATENT LEGAL ADMINISTRATION - CRYSTAL PLAZA 3/4-3D65